UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner

U.S. Patent No.: 8,974,790
Issue Date: Mar. 10, 2015
Title: Methods of Administering Anti-TNFα Antibodies

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,974,790 PURSUANT TO 35 U.S.C. §§311-319 AND 37 C.F.R. §42

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Ex. No.[1]	Description	Referred To As	Reference Type[2]
1001	United States Patent No. 8,974,790, filed May 30, 2014, issued Mar. 10, 2015	"'790 patent"	n/a
1002	Declaration of Simon M. Helfgott, M.D.	"Helfgott Decl."	n/a
1003*	B. A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM (1999) (ACR Abstract Concurrent Session, RA: TNF Blockade, Wed., Nov. 17, 1999 S400)	"VDP1999"	102(b)
1004	Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 ANNALS RHEUMATIC DISEASES I70 (1999)	"Kempeni"	102(b)
1005	William J. Sandborn & Stephen B. Hanauer, *Antitumor Necrosis Factor Therapy for Inflammatory Bowel Disease: A Review of Agents, Pharmacology, Clinical Results, and Safety*, 5 INFLAMMATORY BOWEL DISEASES 119 (1999)	"Sandborn"	102(b)
1006*	WO 97/29131, filed Feb. 10, 1997, published Aug. 14, 1997	"Salfeld"	102(b)
1007	2001 PHYSICIAN'S DESK REFERENCE (55th ed., published Nov. 2000[3]) (excerpts)	"2001 PDR"	102(a)

[1] Pincites in the Petition and Declarations to exhibits marked with an asterisk (*) refer to stamped on page numbers. All other pincites in the Petition and Declarations are to original page numbers.

[2] This column indicates whether an exhibit is prior art under 35 U.S.C. §§102(a), (b) or (e). "n/a" indicates the exhibit is not being relied upon as prior art.

[3] *See* ex.1048 (stating that the 2001 Physician's Desk Reference was published in November 2000).

Ex. No.[1]	Description	Referred To As	Reference Type[2]
1008	Declaration of Dr. Ingvar Bjarnason, M.D.	"Bjarnason Decl."	n/a
1009*	WO 98/05357, filed Aug. 1, 1997, published Feb. 12, 1998	"Feldmann"	102(b)
1010*	Notice of Allowability, SN 14/292,707 (Jan. 2, 2015)	"Notice of Allowability"	n/a
1011*	WO 99/65867, filed June 17, 1999, published Dec. 23, 1999	"WO '867"	102(b)
1012*	WO 98/52941, filed May 22, 1998, published Nov. 26, 1998	"WO '941"	102(b)
1013*	WO 99/58502, filed May 11, 1999, published Nov. 18, 1999	"WO '502"	102(b)
1014	United States Patent No. 5,760,068, PCT filed Nov. 14, 1994, issued June 2, 1998	"'068 patent"	102(b)
1015	Declaration of John Posner, Ph.D.	"Posner Decl."	n/a
1016	Douglas J. Perkins et al., *Reduction of NOS2 Overexpression in Rheumatoid Arthritis Patients Treated with Anti-Tumor Necrosis Factor α Monoclonal Antibody (cA2)*, 41 ARTHRITIS & RHEUMATISM 2205 (1998)	"Perkins"	102(b)
1017*	R. Rau et al., *Experience with D2E7*, 25 RHEUMATOLOGY TODAY 83 (2000)	"Rau"	102(a)[4]
1018	Remicade™ (infliximab) 1998 Package Insert (Centocor, Inc. Aug. 1998)	"Remicade® 1998 Package Insert"	102(b)
1019	R. Rau, et al., *Erfahrungen mit D2E7*, 25 AKT RHEUMATOL 83 (2000) (German Original)	"Rau – German Translation"	102(a)[5]

[4] In IPR2016-00172, the Patent Owner herein asserted and relied on Rau as prior art to related U.S. Patent 8,889,135, which has the same priority date as U.S. Patent 8,974,790, the subject of this Petition. Ex.1105 at 50; Ex.1069 at 11. Additionally, Rau was asserted as prior art in IPR2016-00408 (also directed to U.S. Patent 8,889,135) without objection from the Patent Owner, and the Board based its findings of invalidity on Rau as a prior art reference. *Boehringer Ingelheim Int'l GMBH v. AbbVie Biotech Ltd.*, No. IPR2016-00408 (P.T.A.B. July 6, 2017).

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1020	Remicade® (infliximab) Package Insert (Centocor, Inc. revised Dec. 2000)	"Remicade® 2000 Package Insert"	102(a)
1021	United States Patent No. 9,017,680, filed Nov. 14, 2014, issued Apr. 28, 2015	"the '680 patent"	n/a
1022	Hendrik M. van Dullemen et al., *Treatment of Therapy-Resistant Perineal Metastatic Crohn's Disease After Proctectomy Using Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody, cA2*, 41 DISEASES COLON & RECTUM 98 (1998)	"van Dullemen 1998"	102(b)
1023	William J. Sandborn et al., *An Engineered Human Antibody to TNF (CDP571) for Active Crohn's Disease: A Randomized Double-Blind Placebo-Controlled Trial*, 120 GASTROENTEROLOGY 1330 (May 2001)	"Sandborn II"	102(a)
1024	P. Rutgeerts et al., *Retreatment with Anti-TNF-α Chimeric Antibody (cA2) Effectively Maintains cA2-Induced Remission in Crohn's Disease*, 112 GASTROENTEROLOGY A1078 (1997) (supplement)	"Rutgeerts"	102(b)
1025	E. C. C. Rankin et al., *The Therapeutic Effects of an Engineered Human Anti-Tumour Necrosis Factor Alpha Antibody (CDP571) in Rheumatoid Arthritis*, 34 BRIT. J. RHEUMATOLOGY 334 (1995)	"Rankin"	102(b)

[5] Ex.1019 is the original German article and ex.1017 is the English translation that AbbVie relied on in the '135 IPR (No. IPR2016-00172), as demonstrated by AbbVie's ex.2115, which includes a declaration. Ex.1017***** at 11.

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1026	Ernest H.S. Choy et al., *The Engineered Human Anti-Tumor Necrosis Factor-α Antibody CDP571 Inhibits Inflammatory Pathways But Not T Cell Activation in Patients with Rheumatoid Arthritis*, 26 J. RHEUMATOLOGY 2310 (1999)	"Choy"	102(b)
1027	SLEISENGER & FORDTRAN'S GASTROINTESTINAL AND LIVER DISEASE: PATHOPHYSIOLOGY, DIAGNOSIS, MANAGEMENT vol. 2 (Mark Feldman et al. eds., 6th ed. 1998)	"Sleisenger & Fordtran's Gastrointestinal and Liver Disease"	102(b)
1028	*Depo-Medrol*, 2017 Physician's Desk Reference, *available at* http://www.pdr.net/drug-summary/Depo-Medrol-Single-Dose-methylprednisolone-acetate-3436.2551	"2017 PDR"	n/a
1029	TEXTBOOK OF RHEUMATOLOGY vol. 1 (William N. Kelley et al. eds., 4th ed. 1993)	"Kelley's Textbook"	102(b)
1030	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172, Patent Owner's Response, Paper No. 37 (Sept. 13, 2016)	"Patent Owner's Response in '135 IPR"	n/a
1031*	Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug That Toppled Lipitor as No. 1*, XCONOMY (Apr. 16, 2012), *available at* http://www.xconomy.com/national/2012/04/16/abbotts-humira-the-3rd-in-class-drug-that-toppled-lipitor-as-no-1/#	"Timmerman"	n/a
1032	Ute Kettritz et al., *Crohn's Disease: Pilot Study Comparing MRI of the Abdomen with Clinical Evaluation*, 21 J. CLINICAL GASTROENTEROLOGY 249 (1995)	"Kettritz"	102(b)
1033	WTS Article Delivery Cover Page (Apr. 11, 2017)	"WTS Cover Page"	n/a

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1035	*Amgen Inc. v. AbbVie Biotech. Ltd.*, No. IPR2015-01517 (Patent Owner's Preliminary Response Oct. 19, 2015)	"Prelim. Response in '158 IPR"	n/a
1036	A. M. Denman, *Rheumatoid Arthritis: Aetiology*, 4 BRIT. MED. J. 601 (1970)	"Denman"	102(b)
1037	Rodrick J. Chiodini et al., *Possible Role of Mycobacteria in Inflammatory Bowel Disease: I. An Unclassified* Mycobacterium *Species Isolated from Patients with Crohn's Disease*, 29 DIGESTIVE DISEASES & SCI. 1073 (1984)	"Chiodini"	102(b)
1038	W. E. W. Roediger, *A New Hypothesis for the Aetiology of Crohn's Disease−Evidence from Lipid Metabolism and Intestinal Tuberculosis*, 67 POSTGRADUATE MED. J. 666 (1991)	"Roediger"	102(b)
1039	Robert W. Chandler et al., *Serological Investigations for Evidence of an Infectious Aetiology of Rheumatoid Arthritis*, 30 ANNALS RHEUMATIC DISEASES 274 (1971)	"Chandler"	102(b)
1040	Joel B. Baseman & Joseph G. Tully, *Mycoplasmas: Sophisticated, Reemerging, and Burdened by Their Notoriety*, 3 EMERGING INFECTIOUS DISEASES 21 (1997)	"Baseman"	102(b)
1041	Joseph Holoshitz et al., *Isolation of $CD4^-$ $CD8^-$ Mycobacteria-Reactive T Lymphocyte Clones from Rheumatoid Arthritis Synovial Fluid*, 339 NATURE 226 (1989)	"Holoshitz 1989"	102(b)

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1043	Michael T. Collins et al., *Results of Multiple Diagnostic Tests for* Mycobacterium avium *subsp.* paratuberculosis *in Patients with Inflammatory Bowel Disease and in Controls*, 38 J. CLINICAL MICROBIOLOGY 4373 (Dec. 2000)	"Collins"	102(a)
1044	G. A. W. Rook et al., *A Reappraisal of the Evidence that Rheumatoid Arthritis and Several Other Idiopathic Diseases are Slow Bacterial Infections*, 52 ANNALS RHEUMATIC DISEASES S30 (1993)	"Rook"	102(b)
1045	R. G. White & J. Gordon, *Adjuvant-Activity of 'Diphtheroid' Organisms Isolated from the Joints of Cases of Rheumatoid Arthritis*, 7 CLINICAL & EXPERIMENTAL IMMUNOLOGY 139 (1970)	"White"	102(b)
1046	Joseph Holoshitz et al., *T Lymphocytes of Rheumatoid Arthritis Patients Show Augmented Reactivity to a Fraction of Mycobacteria Cross-Reactive with Cartilage*, 2 LANCET 305 (1986)	"Holoshitz 1996"	102(b)
1047	Pieter C. M. Res et al., *Synovial Fluid T Cell Reactivity Against 65 kD Heat Shock Protein of Mycobacteria in Early Chronic Arthritis*, 2 LANCET 478 (1988)	"Res"	102(b)
1048	https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752	n/a	n/a

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1049	United States Patent No. 9,090,689, filed Apr. 8, 2015, issued July 28, 2015	"'689 patent"	n/a
1050	Larry W. Moreland, *Inhibitors of Tumor Necrosis Factor for Rheumatoid Arthritis*, 26 J. RHEUMATOLOGY 7 (1999)	"Moreland"	102(b)
1051	Remicade® (Infliximab) Package Insert, 2001 Physician's Desk Reference (Centocor, Inc. 1999)	"1999 Remicade® label"	102(b)
1052	Stephan R. Targan et al., *A Short-Term Study of Chimeric Monoclonal Antibody cA2 to Tumor Necrosis Factor α For Crohn's Disease*, 337 NEW ENG. J. MED. 1029 (1997)	"Targan"	102(b)
1053	T. T. MacDonald et al., *Tumour Necrosis Factor-Alpha and Interferon-Gamma Production Measured at the Single Cell Level in Normal and Inflamed Human Intestine*, 81 CLINICAL & EXPERIMENTAL IMMUNOLOGY 301 (1990)	"MacDonald"	102(b)
1054	Nick Di Girolamo et al., *Expression of TNF-α by Human Plasma Cells in Chronic Inflammation*, 61 J. LEUKOCYTE BIOLOGY 667 (1997)	"Di Girolamo"	102(b)
1055	George Kollias et al., *The Function of Tumour Necrosis Factor and Receptors in Models of Multi-Organ Inflammation, Rheumatoid Arthritis, Multiple Sclerosis and Inflammatory Bowel Disease*, 58 ANNALS RHEUMATIC DISEASES I32 (1999)	"Kollias"	102(b)
1056	A. Glennas et al., *Auranofin Is Safe and Superior to Placebo in Elderly-Onset Rheumatoid Arthritis*, 36 BRIT. J. RHEUMATOLOGY 870 (1997)	"Glennas"	102(b)
1057	S. C. Truelove et al., *Comparison of Corticosteroid and Sulphasalazine Therapy in Ulcerative Colitis*, BRIT. MED. J. 1708 (1962)	"Truelove"	102(b)

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1058	Nanna Svartz, *Salazopyrin, A New Sulfanilamide Preparation*, 110 ACTA MEDICA SCANDINAVICA 577 (1942)	"Svartz 1942"	102(b)
1059	N. Svartz, *The Treatment of 124 Cases of Ulcerative Colitis with Salazopyrine and Attempts of Desensibilization in Cases of Hypersensitiveness to Sulfa*, 130 ACTA MEDICA SCANDINAVICA 465 (1948)[6]	"Svartz 1948"	102(b)
1060	A. P. Dick et al., *Controlled Trial of Sulphasalazine in the Treatment of Ulcerative Colitis*, 5 GUT 437 (1964)	"Dick"	102(b)
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1062	Maarten Boers et al., *Randomised Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine with Sulphasalazine Alone in Early Rheumatoid Arthritis*, 350 LANCET 309 (1997)	"Boers"	102(b)
1063*	P.A. Bacon et al., *Thermographic Assessment of the Anti-Inflammatory Effect of Flurbiprofen in Rheumatoid Arthritis*, 3 CURRENT MED. RES. & OPINION 20 (1975)	"Bacon"	102(b)
1064	D. S. Rampton & G. E. Sladen, *Prostaglandin Synthesis Inhibitors in Ulcerative Colitis: Flurbiprofen Compared with Conventional Treatment*, 21 PROSTAGLANDINS 417 (1981)	"Rampton 1981"	102(b)
1065	D. S. Rampton & G. E. Sladen, *Relationship Between Rectal Mucosal Prostaglandin Production and Water and Electrolyte Transport in Ulcerative Colitis*, 30 DIGESTION 13 (1984)	"Rampton 1984"	102(b)

[6] See ex.1033 for publication information.

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1066*	M. Campieri et al., *Prostaglandins, Indomethacin, and Ulcerative Colitis*, 78 GASTROENTEROLOGY (1980)	"Campieri"	102(b)
1067	Herbert J. Kaufmann et al., *Nonsteroidal Anti-Inflammatory Drugs Activate Quiescent Inflammatory Bowel Disease*, 107 ANNALS INTERNAL MED. 513 (1987)	"Kaufmann"	102(b)
1068	Christian Moens & J. Brocteur, *Treatment of Rheumatoid Arthritis with Immunosuppresive Drugs*, 11 ACTA RHEUMATOLOGICA SCANDINAVICA 212 (1961)	"Moens & Brocteur"	102(b)
1069	*Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172, Patent Owner's Updated Exhibit List (as of January 19, 2017)	"AbbVie's Updated Exhibit List"	n/a
1070	S. Candy et al., *A Controlled Double Blind Study of Azathioprine in the Management of Crohn's Disease*, 37 GUT 674 (1995)	"Candy"	102(b)
1071	http://www.gastrojournal.org/article/S0016-5085(00)84761-7/abstract	n/a	n/a
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1073	Knut Joachim Berg et al., *Side Effects of Cyclosporin A Treatment in Patients with Rheumatoid Arthritis*, 29 KIDNEY INT'L 1180 (1986)	"Berg"	102(b)
1074	A.W.A.M. van Rijthoven et al., *Cyclosporin Treatment for Rheumatoid Arthritis: A Placebo Controlled, Double Blind, Multicentre Study*, 45 ANNALS RHEUMATIC DISEASES 726 (1986)	"van Rijthoven"	102(b)

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1076	Simon Lichtiger et al., *Cyclosporine In Severe Ulcerative Colitis Refractory to Steroid Therapy*, 330 NEW ENG. J. MED. 1841 (1994)	"Lichtiger"	102(b)
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1078	Patricia Clark et al., *Hydroxychloroquine Compared with Placebo in Rheumatoid Arthritis: A Randomized Controlled Trial*, 119 ANNALS OF INTERNAL MED. 1067 (1993)	"Clark"	102(b)
1079	Nicholas F. LaRusso et al., *Prospective Trial of Penicillamine in Primary Sclerosing Cholangitis*, 95 GASTROENTEROLOGY 1036 (1988)	"LaRusso"	102(b)
1080	E. C. Huskisson et al., *Trial Comparing D-Penicillamine and Gold in Rheumatoid Arthritis*, 33 ANNALS RHEUMATIC DISEASES 532 (1974)	"Huskisson 1974"	102(b)
1081	Robert N. Thompson et al., *A Controlled Two-Centre Trial of Parenteral Methotrexate Therapy for Refractory Rheumatoid Arthritis*, 11 J. RHEUMATOLOGY 760 (1984)	"Thompson"	102(b)
1082	Richard A. Kozarek et al., *Methotrexate Induces Clinical and Histologic Remission in Patients with Refractory Inflammatory Bowel Disease*, 110 ANNALS INTERNAL MED. 353 (1989)	"Kozarek"	102(b)

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1084	Brian G. Feagan et al., *Methotrexate for the Treatment of Crohn's Disease*, 332 NEW ENG. J. MED. 292 (1995)	"Feagan I"	102(b)
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1086	E. C. Huskisson et al., *Immunostimulant Therapy with Levamisole for Rheumatoid Arthritis*, 1 LANCET 393 (1976)	"Huskisson 1976"	102(b)
1087	Bruce Miller et al., *Double-Blind Placebo Controlled Crossover Evaluation of Levamisole in Rheumatoid Arthritis*, 23 ARTHRITIS & RHEUMATISM 172 (1980)	"Miller"	102(b)
1088	P. Franchimont et al., *Double-Blind Placebo-Controlled Evaluation of Levamisole in Chronic Rheumatoid Arthritis*, 8 SCANDINAVIAN J. RHEUMATOLOGY 43 (1979)	"Franchimont"	102(b)
1089	A. W. Segal et al., *Levamisole in the Treatment of Crohn's Disease*, 2 LANCET 382 (1977)	"Segal"	102(b)
1090	Susan V. Onrust & Harriet M. Lamb, *Infliximab: A Review of its Use in Crohn's Disease and Rheumatoid Arthritis*, 10 BIODRUGS 397 (1998)	"Onrust"	102(b)
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1093	United States Patent No. 8,889,135, filed June 5, 2002, issued Nov. 18, 2014	"'135 patent"	n/a
1094	GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Joel G. Hardman et al., eds., 9th ed. 1996)	"Goodman & Gilman's"	102(b)
1095	Ann Gardulf et al., *Subcutaneous Immunoglobulin Replacement in Patients with Primary Antibody Deficiencies: Safety and Costs*, 345 LANCET 365 (1995)	"Gardulf"	102(b)
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[7] See ex.1071 for publication information.

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1101	*Boehringer Ingelheim Int'l GMBH. v. AbbVie Biotech. Ltd.*, No. IPR 2016-00409, Patent Owner's Response, Paper No. 24 (Oct. 28, 2016)	"IPR 2016-00409 Patent Owner's Response"	n/a
1102	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172, Declaration of Alexander A. Vinks (Sept. 13, 2016)	"Vinks Decl."	n/a
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1105	*Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172, Patent Owner's Response, Paper No. 37 (Sept. 13, 2016)	"AbbVie's '135 Response"	n/a
1106	R. Munro & H. Capell, *Prevalence of Low Body Mass in Rheumatoid Arthritis: Association with the Acute Phase Response*, 56 ANNALS RHEUMATIC DISEASES 326 (1997)	"Munro"	102(b)
1107*	B. A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 ANNALS RHEUMATIC DISEASES (July 2000) [OP056]	"VDP2000"	102(a)

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1109*	R. Rau et al., *Long-Term Treatment with the Fully Human Anti-TNF-Antibody D2E7 Slows Radiographic Disease Progression in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM S400 (1999)	"Rau 1999"	102(b)
1110*	Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in Patiens [sic] with Rheumatoid Arthritis – Results of a Phase I Study*, 41 ARTHRITIS & RHEUMATISM S57 (1998)	"Schattenkirchner"	102(b)
1111*	FDA, Memorandum, Review of BLA Submission 99-O 128 (Oct. 22, 1999)	"BLA Submission"	n/a
1112	Letter from Karen D. Weis, Director, Division of Clinical Trial Design and Analysis, to Martin Page, Centocor, Inc. (Nov. 10, 1999), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1999/inflcen111099L.htm	"Remicade® Approval Letter"	n/a
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1116	R. C. Evans et al., *Treatment of Ulcerative Colitis with an Engineered Human Anti-TNFα Antibody CDP571*, 11 ALIMENT PHARMACOLOGY & THERAPEUTICS 1031 (1997)	"Evans"	102(b)
1117	Brian R. Stotland & Gary R. Lichtenstein, *Newer Treatments for Inflammatory Bowel Disease*, 34 DRUGS TODAY 177 (1998)	"Stotland"	102(b)
1118	Robert W. Summers et al., *National Cooperative Crohn's Disease Study: Results of Drug Treatment*, 77 GASTROENTEROLOGY 847 (1979)	"Summers"	102(b)
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1120	A. Hermanowicz et al., *Controlled Therapeutic Trial of Levamisole and Sulphasalazine in Acute Ulcerative Colitis*, 25 GUT 534 (1984)	"Hermanowicz"	102(b)
1121*	Edouard Louis & Jacques Belaïche, *Hydroxychloroquine (Plaquenil®) for Recurrence Prevention of Crohn's Disease After Curative Surgery*, 19 GASTROENTÉROLOGIE CLINIQUE ET BIOLOGIQUE 233 (1995)	"Louis"	102(b)
1122	Paul Rutgeerts et al., *A Comparison of Budesonide with Prednisolone for Active Crohn's Disease*, 331 NEW ENG. J. MED. 842 (1994)	"Prednisolone"	102(b)
1123	Subrata Ghosh et al., *Ulcerative Colitis* 320 BRIT. MED. J. 1119 (April 2000)	"Ghosh"	102(b)

Ex. No.[1]	Description	Referred To As	Reference Type[2]
1124*	J.-M Reimund et al., *Mucosal Inflammatory Cytokine Production by Intestinal Biopsies in Patients with Ulcerative Colitis and Crohn's Disease*, 16 J. CLINICAL IMMUNOLOGY 144 (1996)	"Reimund"	102(b)
1125	Jørn Brynskov et al., *Cytokines (Immunoinflammatory Hormones) and Their Natural Regulation in Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis): A Review*, 12 DIGESTIVE DISEASES 290 (1994)	"Brynskov"	102(b)
1126	Remicade® (infliximab) Package Insert (Centocor, Inc., revised Sept. 12, 2005)	"2005 Remicade® Label"	n/a
1127	Brian McConkey et al., *Effects of Gold, Dapsone, and Prednisone on Serum C-Reactive Protein and Haptoglobin and the Erythrocyte Sedimentation Rate in Rheumatoid Arthritis*, 38 ANNALS RHEUMATIC DISEASES 141 (1979)	"McConkey"	102(b)
1128	K. Fellermann et al., *Mycophenolate Mofetil: Lack of Efficacy in Chronic Active Inflammatory Bowel Disease*, 14 ALIMENTARY PHARMACOLOGY & THERAPY 171 (2000)[8]	"Fellermann"	102(b)
1129	http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2036.2000.00695.x/full	n/a	n/a

[8] Fellermann was published in February 2000. *See* ex.1129.

I. INTRODUCTION

AbbVie Biotechnology Ltd.'s ("AbbVie") U.S. Patent No. 8,974,790 (the "'790 patent," ex.1001[9]) claims a method for treating ulcerative colitis ("UC") by the subcutaneous administration of 40mg of a human anti-TNF-α antibody identified by recited amino acid sequences, which the specification states may be found in the light and heavy chains of an antibody termed "D2E7,"[10] once every 13-15 days (*i.e.*, "every other week" or "eow") for a period of time sufficient to treat UC. According to AbbVie, the term D2E7 encompasses adalimumab, the active ingredient in its Humira® product.[11]

Subcutaneously administering 40mg D2E7 eow to treat rheumatoid arthritis ("RA") is obvious over the prior art as the Board has already determined. The UC 40mg D2E7 dosing regimen claimed in the '790 patent is exactly the same dosing regimen claimed for treating RA with D2E7 in AbbVie's earlier-issued patent, U.S. Patent No. 8,889,135 (the "'135 patent," ex.1093), with which it shares a common specification, having been filed as a "division" of the application that

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[9] Pincites in the Petition and Declarations to exhibits marked with an asterisk (*) refer to stamped-on page numbers. All other pincites in the Petition and Declarations are to original page numbers.

[10] For the purposes of this Petition only, the claimed antibody will be termed "D2E7" without prejudice to Sandoz's ability to challenge the meaning, scope, and indefiniteness of the term in other proceedings.

[11] *See, e.g.*, ex.1049 (AbbVie's U.S. Patent No. 9,090,689) at 11:56-57 ("D2E7, also referred to as HUMIRA® and adalimumab . . . .").

issued as the ’135 patent. As set forth in this Petition and accompanying declarations, eow subcutaneous dosing of 40mg of D2E7 to treat RA, as claimed in the ’135 patent, is obvious over either of two combinations of AbbVie prior art references: (1) van de Putte 1999 (“VDP1999,” ex.1003) and Kempeni (ex.1004); or (2) van de Putte 2000 (“VDP2000,” ex.1107) and Rau (ex.1017). Sandoz Inc.’s (“Sandoz” or “Petitioner”) position is fully supported by the Board’s May 16, 2017 and July 6, 2017 Final Written Decisions (“FWDs”) in IPR2016-00172 (“*Coherus*”) [12], IPR2016-00408 (“*BI408*”), and IPR2016-00409 (“*BI409*”), finding that the claims of the ’135 patent are invalid over these same two prior art combinations. *See* exs. 1003, 1004, 1017, 1107.

The only difference between the only independent claim of the ’790 patent and claim 1 of the ’135 patent invalidated by the Board, is that the words “ulcerative colitis” are substituted for “RA.” However, the prior art taught treating both UC and RA by administering drugs, including TNF-α inhibitors, using the same dosing regimens. AbbVie’s own prior art Salfeld published patent

[12] The Board also invalidated two other AbbVie patents claiming the D2E7 dosing regimen of 40mg subcutaneously administered eow to treat RA (U.S. Patent Nos. 9,017,680 (the “’680 patent,” ex.1021) and 9,073,987 (the “’987 patent,” ex.1098). *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00188, FWD, Paper No. 54 (P.T.A.B. June 9, 2017); *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00189, FWD, Paper No. 56 (P.T.A.B. June 9, 2017). The decisions invalidating the ’680 and ’987 patents also rely on VDP1999 and Kempeni and set forth substantially the same reasoning as the *Coherus* decision with respect to the ’135 patent.

application disclosed treating both RA and UC, which together with Crohn's disease ("CD") is encompassed within inflammatory bowel disease ("IBD"), with the same D2E7 dosage range. Ex.1006***** at 39:13-15, 41:19, 35:31-32. In fact, the only disclosure in the '790 patent relating to UC was copied directly from Salfeld. *Compare* ex.1001 at 27:14-25 *with* ex.1006***** at 41:14-25. Therefore, every element of the '790 patent's claims was disclosed by AbbVie's own prior art references.

As Petitioner's experts demonstrate, a person of ordinary skill in the art ("POSA") would have been motivated to use the subcutaneous 40mg eow RA D2E7 dosing regimen to treat UC and would have had a reasonable expectation of success because the prior art (*e.g.*, Sandborn, ex.1005) taught that the anti-TNF-α antibodies infliximab and CDP571 were effective in treating RA and IBD (both CD and UC) using the same dosage ranges, and for the more advanced infliximab trials for RA and CD, further showed that the same dosing intervals had been used for repeat dosing. Moreover, even before the development of anti-TNF-α inhibitors, the prior art had taught that numerous drugs were useful to treat RA and IBD using the same dosing regimens. In addition, due to the chronic nature of RA and IBD, a POSA understood that the course of treatment often included dosing over extended periods of time (*i.e.*, years). *See infra* VI.C.5.

AbbVie confirmed this motivation and expectation of success. When it obtained the D2E7 UC treatment claims in the '790 patent, it did so based solely upon data for treating RA with D2E7. The only working examples relate to the treatment of RA, and the specification contains no information on any dosing regimen specific to UC. AbbVie used the RA dosing regimen to support its UC dosing regimen claims, exactly as a POSA would have done based on the prior art.

Therefore, it would have been obvious for a POSA to have used the prior art D2E7 dosing regimen that the Board found obvious to treat RA – 40mg D2E7 subcutaneously administered eow – to also treat UC.

Accordingly, pursuant to 35 U.S.C. §§311-319 and 37 C.F.R. §42, Sandoz respectfully requests *inter partes* review ("IPR") of all claims (*i.e.*, claims 1-6) of the '790 patent to Fischkoff et al., titled "Methods of Administering Anti-TNFα Antibodies" (ex.1001), which is currently assigned to AbbVie.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(a)(1)

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Sandoz is the real party-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

1. Related Litigation

AbbVie has asserted U.S. Patent Nos. 8,663,945; 8,911,964; 8,916,157; 8,961,973; 8,986,693; 9,096,666; 9,220,781; 9,272,041; 9,359,434; and 9,365,645 in the following litigation in which Petitioner was not and is not a party: *AbbVie*

Inc. et al. v. Amgen Inc. et al., No. 1:16-cv-00666-MSG (D. Del. filed Aug. 4, 2016). AbbVie has also asserted U.S. Patent Nos. 8,926,975; 9,018,361; 9,090,867; 9,096,666; 9,255,143; 9,266,949; 9,272,041; and 9,546,212 in the following litigation in which Petitioner was not and is not a party: *AbbVie Inc. et al. v. Boehringer Ingelheim Int'l GMBH et al.*, 1:17-cv-01065-MSG (D. Del. Filed Aug. 2, 2017). Of the patents asserted by AbbVie in the identified litigations, only U.S Patent No. 9,546,212 and the '790 patent claim priority to the same applications. Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '790 patent.

2. Related Proceedings Before the Board

The '790 patent is related to the subjects of the following administrative matters, which may affect, or be affected by, a decision in this proceeding: (1) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00172 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated November 9, 2015; (2) *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00408 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (3) *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00409 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (4) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-

00188 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,017,680, dated December 7, 2015; (5) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00189 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,073,987, dated December 7, 2015. On May 17, 2016, the Board instituted *inter partes* review for Case No. IPR2016-00172. On June 13, 2016, the Board issued decisions instituting *inter partes* review for Case Nos. IPR2016-00188 and IPR2016-00189. On July 7, 2016, the Board instituted *inter partes* review for Case Nos. IPR2016-00408 and IPR2016-00409.

On May 16, 2017, the Board issued a FWD in IPR No. 2016-00172 on the ’135 patent (*Coherus*). On June 9, 2017, the Board issued FWDs in IPR Nos. IPR2016-00188 and IPR2016-00189 on the ’680 and ’987 patents, respectively. All three patents were directed to a method of treating RA by administering 40mg D2E7 subcutaneously eow. Ex.1093 at claim 1, Ex.1021 at claim 1, Ex.1098 at claim 1. In its decisions, the Board found the claims of all three patents invalid over VDP1999 and Kempeni.

On July 6, 2017, the Board issued FWDs in Nos. IPR2016-00408 and IPR2016-00409. In IPR2016-00408, the Board found the claims of the ’135 patent unpatentable over VDP2000 (ex.1107) and Rau (ex.1017). In IPR2016-00409, the Board found the claims of the ’135 patent obvious over VDP1999 (ex.1003) and

Kempeni 1999 (ex.1004), and alternatively over Rau 1998, Schattenkirchner 1998, and VDP1999 (ex.1003).

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Lead Counsel	Back-up Counsel
David K. Barr (Reg. No. 31,940) David.Barr@apks.com Arnold & Porter Kaye Scholer LLP 250 W. 55th Street New York, NY 10019 T: 212-836-7560 F: 212-836-6560	Daniel Reisner (*pro hac vice* motion to be filled) Daniel.Reisner@apks.com Arnold & Porter Kaye Scholer LLP 250 W. 55th Street New York, NY 10019 T: 212-836-8132 F: 212-836-6432

D. Service Information (37 C.F.R. §42.8(b)(4))

Please address all correspondence to the lead and backup counsel at the contact information above. Petitioner also consents to service by email at David.Barr@apks.com and Daniel.Reisner@apks.com.

E. Fee Payment Authorization (37 C.F.R. §42.103(a))

Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 502387 for the fees set in 37 C.F.R. §42.15(a) for this Petition for IPR, and further authorizes payment of any additional fees to be charged to this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. §42.104(a))

As required by 37 C.F.R. §42.104(a), Petitioner certifies that the '790 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR on the ground identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. §42.104(b))

A. Effective Filing Date of the '790 Patent

The '790 patent issued March 10, 2015 from SN 14/292,707 filed May 30, 2014, which on the face of the '790 patent is stated to be a "[d]ivision" of SN 10/163,657, filed June 5, 2002. Ex.1001. The '790 patent claims priority to provisional application No. 60/296,961, filed June 8, 2001. *Id.* For purposes of this petition only, the effective filing date of the challenged claims is June 8, 2001.

B. The Prior Art and Statutory Ground of the Challenge (37 CFR §42.104(b)(2))

Petitioner requests IPR and cancellation of claims 1-6 of the '790 patent on two grounds pursuant to pre-AIA 35 U.S.C. §103. In accordance with 37 C.F.R. §42.6(c), the Petition has been filed with the exhibits and the declarations of Ingvar Bjarnason, M.D. (ex.1008), John Posner, Ph.D. (ex.1015), and Simon Helfgott, M.D (ex.1002).

Claims 1-6 are invalid over either (1) Salfeld (ex.1006), Sandborn (ex.1005), Kempeni (ex.1004) and VDP1999 (ex.1003); or (2) Salfeld (ex.1006), Sandborn (ex.1005), VDP2000 (ex.1107) and Rau (ex.1017).

The publications in Ground 1 are all prior art under pre-AIA 35 U.S.C. §102(b) because each issued or published more than one year before the assumed

effective filing date (June 8, 2001). VDP2000 and Rau are prior art under pre-AIA 35 U.S.C. §102(a).[13]

Table 1. Grounds for *Inter Partes* Review

The challenged claims are unpatentable based upon the following grounds:

Ground	Claims	Statutory Basis and Prior Art
1	1-6	Obvious under §103(a) over Salfeld combined with Kempeni and VDP1999, in view of Sandborn
2	1-6	Obvious under §103(a) over Salfeld combined with VDP2000 and Rau, in view of Sandborn

Sandoz's declarations further describe the grounds for the invalidation of the '790 patent. Bjarnason is an expert in the field of gastroenterology with over 35 years of experience in treating UC and CD patients. Ex.1008 at ¶¶3-9. Posner is a clinical pharmacologist, medical professor, and drug development expert with more than three decades of experience in the development of both small molecule and biologic pharmaceuticals. Ex.1015 at ¶¶3-17. Helfgott is an expert in the field of rheumatology. Ex.1002 at ¶¶3-15.

Bjarnason, Posner and Helfgott are qualified to provide opinions as to what a POSA would have understood, known, or concluded from the prior art in their respective fields and are therefore competent to testify in this proceeding. Ex.1002 at ¶¶3-26; Ex.1008 at ¶¶3-9, 19-25; Ex.1015 at ¶¶3-18, 31-35. Many of the prior

[13] AbbVie asserted Rau was prior art in IPR2016-00172 (ex.1105 at 50) and did not challenge the prior art status of VDP2000 and Rau in IPR2016-00408.

art references cited herein are articles and abstracts that were published in medical journals. As Bjarnason explains, over the course of his career he has subscribed to many such journals and/or has accessed them in libraries or from online databases. Ex.1008 at ¶10. In his experience, journal issues are available to the public (either through the mail to subscribers, including libraries, or online when published over the internet), as of approximately the date printed on the face of the reference, if not slightly earlier. *Id.*

V. SUMMARY OF THE '790 PATENT

A. Background of the '790 Patent

The '790 patent issued with six claims. Claim 1, the only independent claim, recites:

> [a] method for treating ulcerative colitis in a human subject, comprising administering subcutaneously to a human subject having ulcerative colitis a total body dose of 40 mg of a human anti-TNFα antibody once every 13-15 days for a time period sufficient to treat the ulcerative colitis, wherein the anti-TNFα antibody comprises [D2E7].[14]

The sole mention of UC in the specification appears in a list of disorders known in the prior art to be mediated by TNF-α. Ex.1001 at 27:24-25. The specification acknowledges that the prior art taught TNF-α "has been implicated in

[14] The specification states that the sequence information recited in claim 1 corresponds to the amino acid sequences found in D2E7. Ex.1001 at 3:31-41. Salfeld discloses D2E7, including its amino acid sequence. Ex.1006***** at 14:1 – 27:19.

the pathophysiology of [IBDs]." *Id.* at 27:13-15. The exact same text appears in AbbVie's prior art Salfeld patent publication and is the sole mention of UC. Ex.1006***** at 41:15-25.

The '790 specification does not include any UC dosage information, and instead provides dosing information equally applicable to all identified diseases. Ex.1001 at 23:21-24. The '790 specification has no working examples or data of any kind for UC. The only examples in the '790 patent are for RA. *Id.* at 28:1–30:29.

Claim 2 depends from claim 1, further specifying amino acid sequence information for the V_L and V_H chains of D2E7. Claim 3 depends from claim 1, adding the requirement that "the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody." Claims 4, 5 and 6, respectively, depend from claims 3, 2 and 1, each adding the requirement that "the [human] anti-TNFα antibody is administered for a period of at least 24 weeks."

B. The Prosecution History of the '790 Patent

The examiner acknowledged that "it would have been obvious to treat [UC] by subcutaneously administering adalimumab based on the knowledge in the prior art[,]" citing AbbVie's own prior art patent, U.S. Patent No. 6,090,382 ("the '382

patent"). Ex.1010***** at 6.[15] The allowed claims directed to treating UC recited the same dosing regimen as the '135 patent claims directed to treating RA (40mg of adalimumab subcutaneously eow), that the same examiner had allowed, and which the Board found obvious in its May 16, 2017, FWD in *Coherus* and its July 6, 2017, FWDs in *BI408* and *BI409*.

The examiner allowed the '790 patent on two grounds.

First, the examiner relied on the fact that CD and UC are related conditions and that the prior art, FDA-approved label for the chimeric anti-TNF antibody infliximab (marketed as Remicade®) provided a higher dose to treat CD ($5^{mg}/_{kg}$), which along with UC is an inflammatory bowel disease ("IBD"), than to treat RA ($3^{mg}/_{kg}$). Ex.1010***** at 6-7. The examiner concluded based on the infliximab label that a POSA would have thought that treating CD would likely require "as much as 66% more adalimumab" than the amount needed for RA. *Id.* at 7. However, in relying on the Remicade® label, the examiner disregarded the prior art clinical trial record showing that the same dosage regimens of infliximab were effective to treat RA, CD, and UC.

[15] The '382 patent is the U.S. counterpart to Salfeld (ex.1006). Salfeld published August 14, 1997 and is prior art to the '790 patent under pre-AIA §102(b).

Second, the examiner relied on the fact that the '135 patent for RA had been allowed. *Id.* Subsequently, the Board in *Coherus*, *BI408* and *BI409* found these RA treatment claims obvious, which Petitioner further supports in this Petition.

C. Person of Ordinary Skill in the Art

A POSA in the field relevant to the '790 patent would have the skill sets of a pharmacologist having experience with antibody drugs and of physicians treating patients for IBD and RA given the known association between these two diseases acknowledged by the '790 patent and disclosed by the prior art. *See infra* VI.C.3.

The pharmacologist would have a Ph.D. in pharmacology, pharmacokinetics, or a related field and at least 3 years' experience working on the pharmacokinetics/pharmacodynamics of biologic drugs. Ex.1015 at ¶33. The physicians would each have an M.D. and at least 3 years' post-residency experience treating patients for IBD and RA, respectively, including with anti-TNF-α drugs. Ex.1008 at ¶¶22-24; Ex.1002 at ¶26.

D. Challenged Claims and Claim Construction (37 C.F.R. §42.104(b)(1) and (b)(3))

The claim terms are presumed to have their ordinary and customary meanings based on the broadest reasonable interpretation ("BRI") of the claim language. 37 C.F.R. §42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278-79 (Fed. Cir. 2015).

The preamble to claim 1 of the '790 patent recites "a method for treating UC in a human subject." Ex.1001. Petitioner submits that this phrase is a statement of intended use and is non-limiting. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003). This is consistent with the Board's *Coherus* decision on the '135 patent (which has the same preamble phrase for RA). *Coherus* at 6; *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172, Decision Institution of *Inter Partes* Review, at 7-8 (P.T.A.B. May 17, 2016).

Claim 1 further recites that the human anti-TNF-α antibody is administered "for a time period sufficient to treat the [UC]." Consistent with the Board's decisions on the '135 patent, Petitioner submits that this phrase does not require a specific level of efficacy and should be accorded its ordinary meaning of "for a time period sufficient to reduce the signs and/or symptoms of UC," which, as explained by Bjarnason, is consistent with how those skilled in the art use "treating" as it relates to UC patients. Ex.1008 at ¶¶26-28; *see Coherus* at 6-9.[16]

[16] In its May 16, 2017 FWD on the '135 patent, the Board confirmed the claim construction set forth in its May 17, 2016 decision to institute IPR. *Coherus* at 8-10. Unlike in RA, where "progression" is measured in terms of pathological changes in the affected joints that are visible by x-ray imaging, in UC there is no analogous, standardized measure of disease progression. Ex.1008 at ¶28. Accordingly, Petitioner's proposed claim construction for the '790 patent does not include "progression" of the disease.

Petitioner's position regarding claim scope is without prejudice to an assertion regarding the appropriate claim scope in other adjudicative forums where a different claim interpretation standard may apply.

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED (37 C.F.R. §42.104(b)(4) and (b)(5))

This petition meets the threshold requirement for IPR because it establishes "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. §314(a).

A. Summary of Argument

The '790 patent claims are directed to methods for treating UC by the subcutaneous administration of 40mg D2E7 eow. This is exactly the same dosing regimen claimed for treating RA in AbbVie's '135 patent, of which the '790 is a divisional. As explained by Posner and confirmed by the Board in *Coherus,* the subcutaneous administration of 40mg D2E7 eow to treat RA, as claimed in the '135 patent, is obvious over either (1) VDP1999 and Kempeni; or (2) VDP2000 and Rau, all AbbVie publications. Ex.1015 at ¶¶123-24.

The only difference between claim 1 of the '790 patent and claim 1 of the '135 patent invalidated by the Board, is that "ulcerative colitis" is substituted for "RA." However Salfeld, AbbVie's own prior art patent, taught that D2E7 was useful in treating IBD (both UC and CD) and RA, and described a D2E7 dosage range ("0.1-20 $^{mg}/_{kg}$, more preferably 1-10 $^{mg}/_{kg}$") applicable to both IBD and RA.

Ex.1006***** at 35:32-33, 39:13-15, 41:20-23. The only disclosure in the '790 patent that relates to UC was lifted directly from Salfeld. *Compare* ex.1001 at 27:14-25 *with* ex.1006***** at 41:14-25. Therefore, all elements of the '790 claims are disclosed in AbbVie's own prior art.

The only new issue in this Petition is whether a POSA would have had the motivation, with a reasonable expectation of success, to use a known drug (D2E7) that was described as useful to treat both RA and UC, to treat UC, using the same dosing regimen that the prior art rendered obvious to treat RA.

Overwhelming evidence demonstrates that a POSA would have been motivated to use the same D2E7 dosage regimen which the prior art rendered obvious to treat RA to also treat UC, and would have had a reasonable expectation of success in so doing. Prior art researchers for decades repeatedly relied on the close relationship between RA and IBD to develop treatments for UC and CD based on RA treatments. Sandborn (ex.1005) described clinical trials for the TNF-α inhibitor infliximab showing that the same dosage amounts were effective to treat RA, UC and CD. Sandborn and a prior art 1999 Remicade® label (ex.1051) also describe clinical trials of infliximab in which both RA and CD patients were treated using the same $10^{mg}/_{kg}$ dose, administered at the same 8-week intervals. In addition, prior art reports on clinical trials for the TNF-α inhibitor CDP571 showed that it was effective in treating all three conditions over a comparable range of

doses: RA ($1^{mg}/_{kg}$, $10^{mg}/_{kg}$), CD ($5^{mg}/_{kg}$, $10^{mg}/_{kg}$, $20^{mg}/_{kg}$), and UC ($5^{mg}/_{kg}$). Ex.1005 at 128; Ex.1099***** at 1; Ex.1008 at ¶¶47, 54, 57, 89-90; *infra* VI.B.3.a. The success demonstrated by treating CD with RA doses and dosing regimens would only further motivate a POSA to use RA doses and dosing regimens for UC because it is so closely related to CD.

The prior art also reveals a long history of treating both RA and IBD with the same therapeutic agents at the same dosage amounts and under the same or comparable dosing regimens. In addition, due to the chronic nature of RA and IBD, a POSA understood that the course of treatment often included dosing over extended periods of time (*i.e.*, years). Ex.1027 at 1754-1755; Ex.1029 at 916 (discussing RA studies where prednisone was administered for years). As Sandoz's expert Bjarnason explains, treatments for IBD followed directly from treatments for RA. Ex.1008 at ¶¶92, 110. Salfeld is an example of this paradigm, describing D2E7 as useful in the treatment of both RA and IBD, among numerous other TNF-α mediated conditions, and providing a description of only a single dosage range for D2E7 applicable to all such conditions. Ex.1006***** at 35:31-33, 38:9–42:17. Accordingly, Salfeld alone taught that D2E7 could be used to treat IBD within a dosing range of 0.1-$20^{mg}/_{kg}$, which includes the claimed 40mg dose, given an average patient weight of either 70 or 80kg. *Id.* at 35:31-33. The prior art

thus described a practice extending back over a half century of using a wide variety of therapeutic agents to treat both RA and IBD with the same dosing regimens.

AbbVie confirms this motivation and expectation of success. The UC treatment claims in the ’790 patent are supported solely by RA examples and data. AbbVie used the RA dosing regimen to support its UC dosing regimen, exactly as a POSA would have done.

Thus, it has been established that the prior art (a) rendered obvious the treatment of RA by subcutaneously administering 40mg D2E7 eow, and (b) taught that UC can be treated using the same therapeutic agents and dosing regimens, including for TNF-α inhibitors, that are effective in treating RA. Accordingly, a POSA would have been motivated to treat UC using the same subcutaneously administered 40mg D2E7 eow dosing regimen known in the art to treat RA, and would have had more than a reasonable expectation that this would successfully treat UC.

B. Patents and Printed Publications Relied on in This Petition

1. Salfeld

Salfeld disclosed the D2E7 antibody (ex.1006***** at 14:1–20:3), its use to treat IBD (CD and UC) (*id.* at 41:14-25) and RA, among other autoimmune diseases (*id.* at 7:36–8:4, 38:33–39:24), its subcutaneous administration (*id.* at 30:5), and a

dosage range of 0.1-20$^{mg}/_{kg}$ applicable to IBD, RA and all other TNF-α-mediated conditions that can be treated with D2E7. *Id.* at 35:31-33.

2. References Teaching Specific Doses of D2E7 Claimed in the '790 Patent

a. VDP1999

VDP1999 described a Phase II study in which patients were given either placebo or 20, 40, or 80mg D2E7 per week subcutaneously for 3 months to treat RA. Ex.1003***** at 3. VDP1999 concluded that "all doses of D2E7 were statistically significantly superior to placebo . . . ." *Id.*

b. Kempeni

Kempeni discussed D2E7 and disclosed several studies demonstrating its efficacy in treating RA. Ex.1004. In a Phase I study, patients received a single D2E7 dose between 0.5$^{mg}/_{kg}$ and 10$^{mg}/_{kg}$ or placebo administered intravenously ("the DE001 study"[17]) "with dose response reaching a plateau at 1 $^{mg}/_{kg}$ D2E7." *Id.* at I71. The doses were well-tolerated. *Id.* Kempeni also disclosed an extension study to DE001 ("DE003") that showed administering D2E7 "every two weeks" was effective. *Id.*

[17] AbbVie used "DE00X" numbers to refer to these clinical studies of D2E7. *See, e.g.*, ex.1017***** at 5. Kempeni describes studies DE001 and DE003, but does not refer to them by those numbers. The study numbers are included here for ease of reference.

Kempeni disclosed another Phase I study ("DE004") "of weekly subcutaneous administration of 0.5 $^{mg}/_{kg}$ D2E7" for three months. *Id.* at I71-72. "[P]lasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." *Id.* at I72. "D2E7 given subcutaneously was safe and as effective as when administered intravenously . . . ." *Id.*

In an additional trial disclosed by Kempeni ("DE010"), patients received a single $1^{mg}/_{kg}$ D2E7 dose administered as either a subcutaneous or intravenous injection. *Id.* Both sets of patients benefited from the treatment and the safety profile of the dose "was comparable to that of placebo." *Id.*

Kempeni concluded that "the fully human anti-TNF-α mAb is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections." *Id.*

c. VDP2000

VDP2000 described an extension of the study described in VDP1999. Ex.1107***** at 2. After month 3 of the VDP1999 study, placebo-treated patients were switched to 40mg D2E7 weekly, while all other doses were continued as randomized (at 20, 40 or 80mg D2E7 weekly). *Id.*

VDP2000 concluded, "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo." *Id.* Further, "20, 40 and

80 $^{mg}/_{week}$ were statistically equally efficacious when given [subcutaneously] in patients with active RA." *Id.* VDP2000 also reported that "[t]he treatment benefit was stable for all parameters over time." *Id.*

d. Rau

Rau described the same clinical studies as Kempeni, and provided additional results. Ex.1017***** at 4-8. It concluded that "D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years." *Id.* at 8. Rau additionally concluded that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." *Id.*

3. Anti-TNF-α Agents Have Been Used To Treat Both RA and IBD Using the Same Doses and Dosing Regimens

a. Sandborn

Sandborn described trials using a single infusion of infliximab to treat RA, UC and CD, and taught that infliximab doses of 5$^{mg}/_{kg}$, 10$^{mg}/_{kg}$ and 20$^{mg}/_{kg}$ were effective in treating RA and both IBD conditions. Ex.1005 at 125, 127-28. It also included data demonstrating that both RA and CD patients could be effectively treated using the same 10$^{mg}/_{kg}$ dose at the same 8 week dosing interval. *Id.* at 126, 128 (describing a CD trial with certain patients receiving 10$^{mg}/_{kg}$ infliximab every 8 weeks at weeks 12, 20, 28 and 36, after having received one or two initial doses,

and an RA trial where certain patients received infliximab "10 $^{mg}/_{kg}$ every 8 weeks for a total of 30 weeks."). Although the UC clinical trials were at an earlier stage than the CD trials (Phase IIa vs. Phase IIb/III) and only involved a single dose study, Sandborn foretold that subsequent UC studies would be conducted to "determine optimal dose and dosing intervals" (*id.* at 129), indicating that infliximab treatment of UC would involve repeat dosing (just like RA and CD treatment) due to the chronic nature of these related conditions. Ex.1008 at ¶¶56, 133.

Sandborn also described RA and IBD clinical trials for CDP571, a humanized anti-TNF monoclonal antibody. Ex.1005 at 119, 127-28. The CDP571 CD and UC trials, according to Sandborn, suggest a "short-term" benefit from CDP571. *Id.* at 127, 129; *see* ex.1116 at 1031 (reporting that a single infusion of $5^{mg}/_{kg}$ CDP571 resulted in "consistent improvement in disease activity" for UC patients). Sandborn also reported that the CDP571 RA clinical trials showed that administering $0.1^{mg}/_{kg}$, $1^{mg}/_{kg}$, or $10^{mg}/_{kg}$ CDP571 resulted in "a dose-related fall in the pain scale at week 1" and reported additional data for 8 weeks. *Id.* at 128. As Bjarnason explains, a POSA would interpret these results as showing that 5 $^{mg}/_{kg}$ was effective in treating CD and UC and that doses from $1^{mg}/_{kg}$ to $10^{mg}/_{kg}$ were effective in treating RA, with the $1^{mg}/_{kg}$ dose being less effective than the 10 $^{mg}/_{kg}$

dose.[18] Ex.1008 at ¶¶118-20. Accordingly, Bjarnason concludes that a POSA would understand from Sandborn that a $5^{mg}/_{kg}$ dose of CDP571 would be intermediate in effect in treating RA between the 1 and $10^{mg}/_{kg}$ doses actually used in the trials and therefore that the same $5^{mg}/_{kg}$ dose of CDP571 would be effective in treating both RA and IBD. *Id.* In addition, Feagan II and Sandborn II separately show that the $10^{mg}/_{kg}$ CDP571 dose described in Sandborn as effective in treating RA was also effective in treating CD.[19] Ex.1099***** at 1; Ex.1023 at 1334.

Accordingly, the prior art taught that TNF-α inhibitors, such as infliximab and CDP571, could be administered to treat both RA and IBD (UC and CD) using the same dosage amounts and the same dosing regimen. Ex.1008 at ¶¶77-91. As the examiner concluded in allowing the '790 patent, a POSA would expect the same dosing regimen used for CD could be used for the related condition UC. *Id.* at ¶66; Ex.1010***** at 6-7. Therefore, the teaching that the same doses and dosing regimens could be used for both RA and CD further reinforced the POSA's

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[18] Rankin (ex.1025), on which Sandborn's discussion of the CDP571 RA clinical trials is based, confirms both the 1 and $10^{mg}/_{kg}$ doses were effective: "[i]n all patients receiving CDP571 there was a fall in the pain scale at week 1 which was dose related." *Id.* at 336 (citation omitted).

[19] Sandborn also described clinical trials for the TNF-α inhibitor etanercept, a human fusion protein now marketed as Enbrel®, but reported that there had been no published clinical trials of etanercept for CD or UC. Ex.1005 at 127, 129.

reasonable expectation that the known RA doses and dosing regimens would also be effective to treat UC. Ex.1008 at ¶91.

b. 1999 Remicade® Label

The 1999 FDA label for Remicade® added an RA indication. Ex.1051 at 1086. It described several clinical trials, including trials using the same $10^{mg}/_{kg}$ dose of infliximab for both RA and CD. *Id.* at 1085-86. Some RA patients were treated with $10^{mg}/_{kg}$ of infliximab at weeks 0, 2, and 6 followed by $10^{mg}/_{kg}$ every 8 weeks (*id.* at 1085) and some CD patients were treated with an initial dose of $10^{mg}/_{kg}$, and 73 patients who remained in clinical response at week 8 were treated with either placebo or $10^{mg}/_{kg}$ at 8 week intervals (weeks 12, 20, 28, 36). *Id.* at 1085-86.

c. Perkins

Perkins described treating RA patients with a single infusion of $5^{mg}/_{kg}$, $10^{mg}/_{kg}$, $20^{mg}/_{kg}$ or placebo. Ex.1016 at 2206. Perkins reported that "[a]dministration of [infliximab] at any dose (i.e., 5[], 10[], or 20 $^{mg}/_{kg}$) was . . . [effective in] RA patients 4 weeks after treatment." *Id.* at 2208.

d. WO 98/05357 ("Feldmann")

Feldmann described treating RA, UC and CD with the same daily dosing range of anti-TNF-α antibodies. Ex.1009***** at 11:12-16, 41:6-10. Feldmann also reported that RA patients were successfully treated with methotrexate and a single

infliximab dose of $5^{mg}/_{kg}$, which is the same dose that has been used to treat CD and UC (ex.1005). Ex.1009***** at 65:14-18, 68:1-6.

e. Sands

Sands reported assessing a single infusion of infliximab at 5, 10, or $20^{mg}/_{kg}$ to treat UC in 11 patients. Ex.1115 at 84-85. The study concluded that infliximab "was well tolerated and may provide clinical benefit to patients with severe, steroid-refractory UC." *Id.* at 88.

C. Ground 1: Salfeld in Combination With Kempeni and VDP1999, in View of Sandborn, Render Claims 1-6 Obvious

The subcutaneous administration of 40mg D2E7 eow to treat RA was obvious over VDP1999 and Kempeni. *See* ex.1015. The only difference between claim 1 of the '790 patent and claim 1 of the '135 patent invalidated by the Board is the substitution of "ulcerative colitis" for "rheumatoid arthritis." However, Salfeld taught that D2E7 was useful to treat both UC and RA with a dosage range applicable to both indications. In fact, the only disclosure in the '790 patent that relates to UC was lifted directly from Salfeld. Therefore, all elements of the '790 patent's claims are disclosed in AbbVie's own prior art.

A POSA would have been motivated to combine (1) Salfeld's teaching that D2E7 could be used to treat UC and RA with the same dosing regimen, as confirmed by the evidence Sandborn described for the TNF-α inhibitor infliximab, with (2) the teachings of Kempeni and VDP1999 that 40mg D2E7 administered

subcutaneously eow was useful to treat RA, and thereby arrive at the method covered by claims 1-6 of the ’790 patent.

1. The Prior Art Taught That It Was Obvious to Administer 40mg Adalimumab EOW to Treat RA

The Board has determined in *Coherus* and *BI409* that the prior art rendered obvious treating RA by subcutaneously administering a 40mg dose of D2E7 eow. For the reasons set forth *infra* VI.C.6, this determination is fully supported by the record evidence. The prior art additionally renders obvious treating UC with that same dosing regimen.

2. Salfeld Taught That D2E7 Can Treat UC With the Same Dose Used to Treat RA

Salfeld disclosed that D2E7 could be subcutaneously administered to effectively treat RA and both UC and CD, along with other TNF-α-mediated conditions. The prior art thus fully supported what the examiner recognized during the ’790 prosecution—“it would have been obvious to treat [UC] by subcutaneously administering adalimumab based on the knowledge in the prior art.” Ex.1010***** at 6.

Salfeld taught that D2E7 can be subcutaneously administered using a dosage range of 0.1 to 20$^{mg}/_{kg}$ applicable to all of the disclosed conditions including RA, UC and CD. Ex.1006***** at 35:31-33, 38:9–42:17; 30:5. Thus, it would have been obvious to treat UC by subcutaneously administering adalimumab eow at the

dosing regimens known to a POSA as useful to treat RA, including 40mg, subcutaneously, eow. This provides the motivation to use the RA dosage regimen to treat UC and a reasonable expectation of success.

3. The Prior Art Taught That TNF-α Inhibitors Could Treat RA and IBD With the Same Dosing Intervals

RA and IBD were known in the prior art to share many characteristics, making them susceptible to similar treatment regimens. These diseases are known to be chronic, remitting-relapsing inflammatory disorders. Ex.1008 at ¶¶61-62.

By the 1990s, researchers had described that TNF-α was implicated in both RA and IBD. *Id.* TNF-α was known to be present in elevated levels in the inflamed joints of RA patients and the inflamed intestinal tissue and serum of IBD patients, and it was widely accepted that the inflammatory mediator played a central role in the pathogenesis of both conditions. *Id.*; Ex.1005 at 120-21. Based on this body of prior art TNF-α research, scientists began evaluating TNF-α-inhibitors to treat both RA and IBD.

Clinical data for the prior art TNF-α inhibitor infliximab confirmed that TNF-α inhibitors were used to treat both RA and IBD using the same or similar dosing regimens. Sandborn described clinical trials of TNF-α inhibitors in treating RA and IBD (UC and CD). Ex.1005. The infliximab clinical trials described by Sandborn showed that the same $5^{mg}/_{kg}$, $10^{mg}/_{kg}$ and $20^{mg}/_{kg}$ dosage amounts were effective to treat both RA and IBD (UC and CD), and demonstrated that the same

dosing interval (every 8 weeks) was effective in treating RA and CD using $10^{mg}/_{kg}$. *Id.* at 125-29.[20] Sandborn described a Phase III infliximab RA study in which 52% of a patient group receiving $10^{mg}/_{kg}$ infliximab every 8 weeks along with methotrexate achieved clinical improvement.[21] *Id.* at 128. Sandborn also described a "preliminary maintenance of remission study . . . as a follow-up to the Phase IIb/III study for chronically active CD" in which "[p]atients who responded to the initial dose of infliximab or placebo, or responded to a second, open label infusion of 10 $^{mg}/_{kg}$ [infliximab]," were treated every 8 weeks with placebo or $10^{mg}/_{kg}$ infliximab beginning at week 12. *Id.* at 126. Sandborn reported that "clinical improvement was maintained" in 35% of the placebo group and in 66% of the $10^{mg}/_{kg}$ group. *Id.* Sandborn concluded that "because the confidence intervals

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[20] Perkins and Feldmann confirm Sandborn's teaching because these references both taught that the same $5^{mg}/_{kg}$ infliximab dose approved to treat CD also effectively treated RA. *See* ex.1016 at 2208 ("Administration of [infliximab] at any dose (i.e., 5 $^{mg}/_{kg}$, 10 $^{mg}/_{kg}$, or 20 $^{mg}/_{kg}$)" was effective to treat RA.); ex.1009***** at 68:1-6 (5, 10, or $20^{mg}/_{kg}$ infliximab "produced clinical responses in the majority of [RA] patients treated . . . ."); ex.1018 at 2 (From the CD study, "[o]ne of twenty-five (4%) placebo patients and thirteen of twenty-seven (48%) patients receiving 5 $^{mg}/_{kg}$ Infliximab achieved a CDAI<150 at week 4.").

[21] In reviewing the data from all patient groups, Sandborn stated that "[t]hese results demonstrated that repeated administration of infliximab was effective for inducing and then maintaining a clinical response in active RA unresponsive to DMARD therapy with methotrexate," and concluded that "infliximab 3 $^{mg}/_{kg}$ administered every 8 weeks, in combination with methotrexate," which achieved a 58% clinical improvement, "was the optimal therapeutic strategy." Ex.1005 at 128.

were wide and the life-table analyses were not statistically significant, the results were not definitive. Nevertheless, the study suggests that infliximab may be effective for maintaining remission for patients who respond to an initial infusion." *Id.* at 127.

As Bjarnason explains, a POSA reading Sandborn would understand that both RA and IBD patients (UC or CD) would likely benefit from even a single 5, 10, or $20^{mg}/_{kg}$ dose of infliximab, and would also likely benefit from the same infliximab dosing regimen of $10^{mg}/_{kg}$ every 8 weeks. Ex.1008 at ¶81. Bjarnason further explained that a POSA would reasonably expect the same RA and CD 8-week dosing interval would also be effective for treating UC with infliximab. *Id.*

Some of these results were also described in the 1999 Remicade® label. Ex.1051 at 1085-86. Figure 1 showed the efficacy of treating RA in a patient group receiving an infliximab dose of $10^{mg}/_{kg}$ administered every 8 weeks (after initial dosing on weeks 0, 2 and 6). *Id.* at 1085.

Similarly, Figure 2 from that label demonstrated that in the first phase of a trial the same infliximab dose of $10^{mg}/_{kg}$ was effective when administered to a patient group. *Id.* at 1086.

The 1999 Remicade® label also described the same CD clinical study described in Sandborn in which patients, after receiving two infliximab doses, received placebo or $10^{mg}/_{kg}$ of infliximab every 8 weeks, although the 1999

Remicade® label did not provide the data set forth in Sandborn. *Id.* For the same reasons described in Sandborn above, the 1999 Remicade® label stated that "[i]n the limited data set available, no significant differences were observed between the REMICADE and placebo re-treated groups." *Id.*

Nevertheless, as Bjarnason concludes, a POSA reading both Sandborn and the 1999 Remicade® label, would understand that infliximab dosed at $10^{mg}/_{kg}$ every 8 weeks would likely be effective in treating the signs and symptoms of both RA and CD, and for that reason would also likely be effective in treating UC. Ex.1008 at ¶81.[22]

As shown below in Table 2, Sandborn and the 1999 Remicade® label reflect what was known to a POSA—that a range of doses of anti-TNF-α agents was effective in treating both RA and IBD and that a POSA should reasonably expect that the *same* dose of an anti-TNF-α agent, such as infliximab, dosed at the same or comparable intervals would be effective for treating both RA and IBD. *Id.* at ¶82.

[22] The fact that not every patient received the same dose, depending on which treatment arm of the study they were in and how they responded to treatment, does not change the fact that the studies demonstrated efficacy at the same doses and dosing intervals for both RA and CD for at least some of the patients in the studies. Ex.1008 at ¶81.

Table 2 – Treating RA and IBD with Infliximab at the Same or Similar Dosing Regimens

Reference	Commonality	RA	IBD	
			CD	UC
Sandborn (ex.1005)[23]	dosing regimen	$10^{mg}/_{kg}$ every 8 weeks for a total of 30 weeks (plus MTX)	$10^{mg}/_{kg}$ every 8 weeks at weeks 12, 20, 28, and 36 after initial dose(s)	
	dosing regimen	single infusion of 5, 10, and $20^{mg}/_{kg}$	same	same
1999 Remicade® label (ex.1051)[24]	dosing regimen	$10^{mg}/_{kg}$ at 0, 2, 6 weeks followed by $10^{mg}/_{kg}$ every 8 weeks thereafter (plus MTX)	after initial dose(s), $10^{mg}/_{kg}$ every 8 weeks (at weeks 12, 20, 28 and 36)	

In addition, Sandborn (ex.1005) provided data from which a POSA would conclude that another anti-TNF-α antibody, CDP571, would be effective in treating both RA and IBD at the same dosages. *Id.* at 127, 128. Sandborn described CDP571 clinical trials in which a $5^{mg}/_{kg}$ dose was found effective in treating IBD

[23] Sandborn disclosed other infliximab dosing intervals for RA not included in this table. Based on the close relationship between RA and IBD treatments that were shown to be effective, a POSA would reasonably expect that each of these dosing regimens would likely be effective to treat IBD. Ex.1008 at ¶¶60-64.

[24] UC trials for infliximab were ongoing and UC was first included in the Remicade® label in 2005 at a dose of $5^{mg}/_{kg}$ at weeks 0, 2, and 6, and every 8 weeks thereafter. Ex.1126 at 33.

(UC and CD) and $1^{mg}/_{kg}$ and $10^{mg}/_{kg}$ doses were found effective in treating RA. *Id*; *supra* VI.B.3.a. As Bjarnason explains, a POSA reading Sandborn would conclude that a CDP571 dose of $5^{mg}/_{kg}$ would not only be effective in treating IBD, but would also be effective in treating RA because that dose is intermediate between the $1^{mg}/_{kg}$ and $10^{mg}/_{kg}$ doses used in the described clinical trials, which demonstrated a "dose-related fall in the pain scale at week 1." Ex.1005 at 128; Ex.1008 at ¶88. While, as Bjarnason further explains, a POSA would have understood from Sandborn that $10^{mg}/_{kg}$ CDP571 would be the most effective described dose for treating RA, a POSA would have concluded that a $5^{mg}/_{kg}$ dose of CDP571 would also have been effective in treating the signs and symptoms of RA. *Id.* Moreover Sandborn, as further supported by either Feagan II or Sandborn II, showed that a $10^{mg}/_{kg}$ dose of CDP571 was effective in treating both RA and CD. Ex.1099***** at 1; Ex.1023 at 1334. Thus, the prior art shows what a POSA would readily understand—that a dose of a TNF-α inhibitor that is effective in treating RA would be expected to also be effective in treating UC. Ex.1008 at ¶91.

4. The Examiner Erred In Overlooking Prior Art Teachings That the Same Doses of Anti-TNF-α Inhibitors Can Be Used to Treat Both RA and IBD

In allowing the claims of the '790 patent to issue, the examiner failed to apply prior art describing the use of the same drugs to treat both RA and IBD with the same dosing regimens. The examiner did acknowledge that dosing for CD

would directly inform likely dosing for UC, however the examiner relied exclusively on the fact that the "Dosage and Administration" section of the FDA-approved label for infliximab (Remicade®) sets forth a higher dosage for CD, $5^{mg}/_{kg}$, than the $3^{mg}/_{kg}$ in combination with methotrexate dosage for RA. Ex.1010***** at 6-7; *see* ex.1020 at 29. Based on this fact alone, the examiner concluded that "one of ordinary skill in the art . . . would have thought that treatment of ulcerative colitis with adalimumab will likely require administering more adalimumab, and potentially as much as 66% more adalimumab, than one would administer to a rheumatoid arthritis patient." Ex.1010***** at 7.

The examiner's conclusion was wrong. The fact that $3^{mg}/_{kg}$ infliximab was selected for inclusion in the "Dosage and Administration" section of the FDA-approved Remicade® label does not render the '790 claims nonobvious, and does not teach away from the '790 claims because the prior art taught that the labeled $5^{mg}/_{kg}$ CD infliximab dose was also effective in treating RA. Ex.1005 at 125, 127.

The examiner applied the wrong standard for obviousness. Obviousness is predicated on the teachings of the prior art, which in this case taught that the same doses of a variety of drugs, including TNF-α inhibitors, can be used to treat the signs and symptoms of RA and IBD. Instead, the examiner focused on infliximab's FDA-approved label dose of $3^{mg}/_{kg}$ for RA, ignoring the prior art teaching that the higher doses of 5 and $10^{mg}/_{kg}$ were also effective to treat RA and

CD. This was error. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) ("There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval. Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications.").[25]

Therefore, the examiner erred in comparing the FDA-approved infliximab doses for RA and CD, and in concluding that a POSA would have assumed that the dose for D2E7 to treat CD should be 66% higher than the D2E7 dose to treat RA. Ex.1010***** at 7.

The fact that the FDA label for infliximab sets forth a higher dose for CD than it does for RA does not teach away from the '790 claims because the prior art taught that the same dosing regimen for TNF-α inhibitors such as D2E7 can be used to treat both RA and IBD. This is especially true where the claims are directed to treating UC without requiring any specific level of efficacy. The prior art showing of infliximab's efficacy at the same doses for both RA and CD not

[25] The examiner's Notice of Allowability made clear that allowance was improperly predicated on the perceived need to know what the FDA-approved dose would be. Ex.1010***** at 6-7. The ability to predict an FDA-approved dose is not the proper standard for obviousness of a claim which only requires the treatment of the signs and symptoms of the specified condition.

only negates the examiner's basis for allowance of the '790 patent, it supports the motivation to use the 40mg eow D2E7 RA dose for CD and UC.[26]

5. Prior to TNF-α Inhibitors, the Same Drugs With the Same Doses and Dosing Regimens Were Used to Treat Both RA and IBD (Including Both UC and CD)

That the same doses and dosing regimens of TNF-α inhibitors can be used to treat both RA and IBD is fully supported by the prior art teaching of using other drugs to treat both diseases with the same doses and dosing regimens. Prior to the development of TNF-α inhibitors, drugs used to treat RA were frequently used for the treatment of IBD at the same or similar doses and dosing regimens. Ex.1008 at ¶¶93-109. As shown in Table 3, steroids, sulphasalazine, NSAIDs, azathioprine, cyclosporine, hydroxychloroquine, penicillamine, methotrexate, and levamisole were all used to treat RA and IBD using similar or identical doses and dosing regimens. *Id.*

Table 3 – Small Molecule Drugs Used to Treat RA and IBD at the Same or Similar Dose

Drug	RA dosing regimen	IBD dosing regimen	
		UC	CD
Prednisolone (ex.1008 at	7.5 or 20 $^{mg}/_{day}$	$20^{mg}/_{day}$	25-40 $^{mg}/_{day}$

[26] Indeed, the very Remicade® label on which the examiner relied when allowing the '790 patent to issue also described in the "Clinical Studies" section that $10^{mg}/_{kg}$ was effective in treating both RA and CD. Ex.1020 at 15-20. As discussed above, the 1999 Remicade® label provides the same clinical data showing that $10^{mg}/_{kg}$ was effective in treating both conditions. Ex.1051 at 1085-86.

¶93)			
Prednisone (*id.*)	15mg daily for two weeks, then 10mg daily	10-60mg (median 20 mg) daily	
Sulphasalazine (*id.* at ¶¶ 94-95)	initially 5-6 $^{g}/_{day}$ maintenance treatment: 2000 $^{mg}/_{day}$	initially up to 6 $^{g}/_{day}$ maintenance treatment: 2 $^{g}/_{day}$	1 $^{g}/_{15\ kg}$ (= 5g for a 75kg person)
Flurbiprofen (*id.* at ¶¶96-97)	200 $^{mg}/_{day}$	200 $^{mg}/_{day}$	N/A
Azathioprine (*id.* at ¶¶98-100)	2.5 $^{mg}/_{kg}/_{day}$	1.5 – 2.5 $^{mg}/_{kg}/_{day}$	1.5 – 4 $^{mg}/_{kg}/_{day}$
Cyclosporine (*id.* at ¶¶101-03)	10 $^{mg}/_{kg}/_{day}$ for 2 months, reduced to 7.5 $^{mg}/_{kg}/_{day}$ during months 3-4 and then 5 $^{mg}/_{kg}/_{day}$ during months 5-6	8.5 $^{mg}/_{kg}/_{day}$ for 5-6 wks or 4 $^{mg}/_{kg}/_{day}$ for at least 10 days 4 $^{mg}/_{kg}/_{day}$ for up to 14 days, if improvement, then oral dose was administered as 6 to 8 $^{mg}/_{kg}/_{day}$ 4 $^{mg}/_{kg}/_{day}$ intravenously comparable with 12-16 $^{mg}/_{kg}/_{day}$ orally	5-7.5 $^{mg}/_{kg}/_{day}$
Hydroxy-chloroquine (*id.* at ¶104)	400 $^{mg}/_{day}$	400 $^{mg}/_{day}$	400 $^{mg}/_{day}$
Penicillamine (*id.* at ¶105)	250-300 $^{mg}/_{day}$, increasing by 250 or 300 mg every fortnight up to total dose of 1-1.8 g daily	Primary sclerosing cholangitis[27]: 250 $^{mg}/_{day}$ increased by 250 $^{mg}/_{day}$ every 4 wks until 750 mg was	N/A

[27] Primary sclerosing cholangitis is associated with UC. Ex.1079 at 1038.

		achieved	
Methotrexate (*id.* at ¶106)	$25^{mg}/_{week}$ and $10^{mg}/_{week}$	$25^{mg}/_{week}$ for 12 weeks, tapered down to $7.5^{mg}/_{week}$	same
Levamisole (*id.* at ¶¶107-09)	150 $^{mg}/_{day}$	150 mg twice a week for the first two weeks, then once a week thereafter	50 mg 8-hourly (= 150 $^{mg}/_{day}$) for 3 consecutive days every 2 weeks

This knowledge is confirmed by prior art patents, which include numerous examples of single dosing ranges being provided to treat both conditions. Ex.1008 at tbl. 3 (discussing exs. 1009, 1011, 1012, 1013, 1014). Moreover, a POSA would know from the small molecule prior art that "[o]nce . . . in remission, [UC] patients are maintained" on the drugs for periods of years. Ex.1027 at 1754-1755; Ex.1008 at ¶113.

Thus, a POSA would approach the development of dosing regimens for a TNF-α inhibitor, including D2E7, with the reasonable expectation of success that a dosing regimen shown to be effective in treating RA would also be effective in treating UC.

6. 40mg D2E7 EOW Dosing to Treat RA is Obvious Over Kempeni and VDP1999

In *Coherus*, the Board determined that the '135 patent's claims to 40mg D2E7 eow subcutaneous dosing to treat RA were obvious over VDP1999 and Kempeni. *Coherus* at 10.[28]

As explained below, the Board's determination was correct and is supported by the evidence set forth in this Petition.

a. VDP1999 and Kempeni Disclose 40mg D2E7 Subcutaneously Dosing EOW to Treat RA

In *Coherus*, the Board held that "[VDP1999] and Kempeni collectively disclose each limitation of the challenged claims." *Id.* at 15. The Board found that VDP1999 disclosed efficacious treatment of RA patients by subcutaneously administering weekly doses of either 20, 40, or 80mg D2E7 for three months. *Id.*; *see* ex.1003***** at 3. VDP1999, according to the Board, disclosed every limitation of claims 1-5 of the '135 patent except for (1) biweekly dosing and (2) administering the antibody for at least 24 weeks. *Coherus* at 15. The Board however concluded that Kempeni explicitly disclosed these two claim limitations which are missing from VDP1999. *Id.* (citing ex.1004 at I71).

Sandoz's expert, Posner, also concludes that the combination of VDP1999 and Kempeni disclose treating RA by subcutaneously administering 40mg

[28] In its FWD in *BI409*, the Board again found the '135 patent invalid over VDP1999 and Kempeni.

adalimumab eow because (1) VDP1999 disclosed 20mg, 40mg, and 80mg D2E7 weekly administered subcutaneously and (2) Kempeni disclosed an intravenous dose ($0.5^{mg}/_{kg}$) of D2E7 equivalent to a subcutaneous dose of 40mg administered eow for 24 weeks. Ex.1015 at ¶¶65-68.

Therefore, for the reasons stated in the Board's *Coherus* and *BI409* opinions and explained by Posner, treating RA by subcutaneously administering 40mg adalimumab eow for at least 24 weeks is obvious over VDP1999 and Kempeni.

b. A POSA Would Have Been Motivated to Combine VDP1999 and Kempeni to Obtain a 40mg Subcutaneously Administered EOW Dose for RA, and Would Have Had a Reasonable Expectation of Success

The Board concluded in *Coherus* that "the ordinarily skilled artisan would have had a reason to select subcutaneous, fixed dosing and a reasonable expectation of success in achieving a subcutaneous fixed dose." *Coherus* at 17.

In *Coherus*, it was not disputed that VDP1999 "reflects the well-known advantages of subcutaneous administration over other forms of administration . . . and fixed dosing over weight-based dosing." *Id.* at 16-17; Ex.1015 at ¶¶65-68, 80-82; Ex.1003***** at 3; Ex.1004 at I72 ("[S]ubcutaneous self administration is a promising approach for D2E7 delivery."). The Board also found no dispute that Kempeni's disclosure that a $0.5^{mg}/_{kg}$ D2E7 dose "is equivalent to a 40 mg fixed dose for an 80kg (*i.e.*, average) patient," including a "40 mg subcutaneous dose."

Coherus at 25; Ex.1015 at ¶67. Kempeni expressly recited that "0.5 to 10 $^{mg}/_{kg}$ D2E7" was administered "'*every two weeks*' until . . . responses could be rated as 'good' . . . ." *Coherus* at 26 (emphasis in original). Thus, "Kempeni also teaches biweekly administration." *Id.* at 25.

Thus the Board concluded that "Kempeni explicitly provides a motivation for converting [VDP1999]'s weekly dosing regimen into a biweekly dosing regimen." *Id.* at 25. In addition, according to the Board, Kempeni suggested that a POSA would have reasonably expected success in using such a dosing regimen over a long time period by "conclud[ing] that long-term treatment with D2E7 in the dose range from 0.5 to $10^{mg}/_{kg}$ 'was well tolerated.'" *Id.* at 25; Ex.1015 at ¶¶46-48.

Similarly, Posner also concludes that a POSA would have had a reason to administer adalimumab by subcutaneous, fixed dosing and would have had a reasonable expectation of success in doing so. Ex.1015 at ¶¶80-85. As Posner explained, VDP1999 discloses subcutaneous administration of D2E7 with a fixed dose (*i.e.*, 20, 40, or 80mg). Ex.1003***** at 3; Ex.1015 at ¶¶65-68, 80-82. Kempeni teaches that intravenous and subcutaneous doses of D2E7 resulted in comparable "plasma concentrations of D2E7." Ex.1004 at I72. Because subcutaneous administration is convenient for a patient who needs to take a drug on a regular basis for a prolonged period of time (ex.1015 at ¶77), a POSA would have a

reasonable expectation of success in combining VDP1999 and Kempeni to design a subcutaneous biweekly fixed dosing regimen. *Id.* at ¶¶65-68, 80-82.

Posner also concludes that a POSA would have been motivated to combine VDP1999 and Kempeni to arrive at a 40mg subcutaneous, eow dosing regimen of D2E7 to treat RA, and would have had a reasonable expectation of success in doing so. *Id.* at ¶¶65-68. Consistent with the Board's findings, Posner explains that Kempeni states that "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks" and "[a]fter six months, 86% of patients continued to receive treatment with D2E7 indicating that long term intravenous treatment with D2E7 . . . was well tolerated" (ex.1004 at I71) which would have motivated a POSA to use Kempeni's biweekly D2E7 dosing regimen.

Therefore, as explained by Posner, a POSA would have been motivated to combine VDP1999 and Kempeni and would have had a reasonable expectation of success in doing so.

c. None of AbbVie's Arguments to the Contrary Have Merit

AbbVie's prior arguments against the combination of VDP1999 and Kempeni are unsupported by the evidence, and were properly rejected by the Board.

AbbVie argued that Kempeni's disclosure that the biweekly phase of the DE003 study was discontinued "once a response was rated as 'good'" and patients

were "retreated 'only upon disease flare up'" taught away from biweekly dosing. *Coherus* at 26-27. But as Posner explains, Kempeni still discloses that patients were effectively dosed biweekly and a POSA would not read Kempeni as discouraging biweekly dosing. Ex.1015 at ¶¶104-05. The Board agreed that this disclosure did not "negate" Kempeni's teaching of biweekly dosing. *Coherus* at 26-27. Posner and the Board agree that the prior art discloses dosing D2E7 subcutaneously in fixed doses (ex.1003***** at 3), and dosing D2E7 on a biweekly schedule (ex.1004 at I71). Ex.1015 at ¶¶37-48; *see Coherus* at 27.

AbbVie also argued that subcutaneous and intravenous doses cannot be compared as Petitioner asserts because their bioavailability differs. *Coherus* at 27. But Posner explains that Kempeni disclosed that "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." Ex.1004 at I72; Ex.1015 at ¶¶99-103. The Board, too, found AbbVie's argument unavailing. *Coherus* at 28.

AbbVie then argued that the fact that the studies disclosed by Kempeni increased the dose for non-responders taught that $0.5^{mg}/_{kg}$ D2E7 did not effectively treat RA. *Id.* at 28-29. However, as Helfgott explains, Kempeni and Rau both teach that the $0.5^{mg}/_{kg}$ dose of D2E7 was sufficient to treat – *i.e.*, reduce the signs symptoms and/or progression – of RA, even if it resulted in only a moderate response. Ex.1002 at ¶¶48-60; *Coherus* at 29. That references disclosed that some

patients lost their response after the $0.5^{mg}/_{kg}$ dose does not teach away from this dosing regimen because the disclosures indicate that there was some reduction in the signs, symptoms, and/or progression of RA. Ex.1002 at ¶¶49-60; *Coherus* at 9, 31.

The Board also considered the issue of anti-drug antibodies ("ADAs"). *Coherus* at 31-38. AbbVie argued that "lower C_{min} values of a subcutaneous 40mg biweekly dose would have triggered concerns about the risk of developing anti-drug antibodies, and that the greater C_{min} and C_{max} fluctuations would have triggered concerns about the safety of that dosing regimen." *Id.* at 32. However, AbbVie's expert "testifie[d] that the publicly available [pharmacokinetic] information in June 2001 would not have permitted a [pharmacokinetic/pharmacodynamics] correlation for modeling purposes, because it did not report patient specific data." *Id.* at 33. Nevertheless, AbbVie's expert conducted modeling. *Id.* The Board agreed "with Petitioner that the conclusions [AbbVie's expert] draws from the modeling are not entitled to much weight because, as both parties note, the minimum effective dose of D2E7 'was undefined in June 2001.'" *Id.* Posner independently reviewed AbbVie's arguments and modeling on ADAs, and reached the same conclusion. Ex.1015 at ¶¶106-121.

As Posner explains, the published prior art clinical data demonstrates that while the risk of ADAs was known, it would not have discouraged a skilled artisan

from pursuing a 40mg biweekly dose of D2E7. *Id.* at ¶¶106-117. Kempeni disclosed that D2E7 was specifically designed to "minimi[ze] antigenicity in humans." Ex.1004 at I70.

AbbVie's expert also asserted that "'large fluctuations between $C_{[max]}$ and $C_{[min]}$ can be hazardous,' particularly if the drug 'has a narrow therapeutic range.'" *Coherus* at 35. However, as Posner explains, D2E7 does not have a narrow therapeutic index, and the prior art indicated that ADAs to D2E7 were not a significant problem. Ex.1015 at ¶¶106-121. The Board also found no evidence to support AbbVie's assertion. *Coherus* at 35 ("Petitioner explains, D2E7 has a wide therapeutic window and a relatively long half-life."); *see* ex.1004 at I71 (reporting that the half-life of D2E7 is 11.6 to 13.7 days and that trials using $0.5^{mg}/_{kg}$ to $10^{mg}/_{kg}$ were safe and efficacious).

7. A POSA Would Have Been Motivated to Combine Salfeld, VDP1999, and Kempeni, in View of Sandborn, to Arrive at the Claimed UC Dosing Regimen

Salfeld and Sandborn provide the motivation to combine the teachings of Salfeld with Kempeni and VDP1999. Salfeld teaches that D2E7 can be used to treat both RA and UC and described a single dosage range for both indications. Ex.1006***** at 35:31-33, 38:34–41:25. Sandborn confirms this, establishing that anti-TNF antibodies are effective in treating both RA and IBD (including both UC and CD) using the same doses and dosing regimens. Ex.1005 at 125-29.

Therefore, a POSA would have been motivated to treat UC with the same 40mg D2E7 eow subcutaneous dosing regimen for RA that the Board found obvious over Kempeni and VDP1999. Ex.1015 at ¶¶65-68; Ex.1008 at ¶¶122-33.

8. A POSA Would Have Had a Reasonable Expectation of Success

A POSA knew from the prior art that drugs that were used to treat RA were also used to treat UC and CD, and that the dosing regimens for RA and UC were either the same or similar. Ex.1008 at VII.D–VII.E.

Salfeld taught that D2E7 could be subcutaneously administered to treat both RA and UC within the same dosing range of 0.1-20$^{mg}/_{kg}$. Ex.1006***** at 35:31-33, 38:34–41:25. As the Board found in the '135 patent IPRs, the subcutaneous administration of 40mg of D2E7 every 13-15 days to treat RA was obvious. *See generally Coherus, BI409*; *supra* VI.C.6; ex.1015 at VII. A POSA would have had every expectation that using the same dosing regimen would be effective to reduce the signs and symptoms of UC. Ex.1008 at ¶121.

This reasonable expectation of success would have been supported by the prior art teaching in Sandborn that (1) TNF-α is implicated in both RA and IBD; (2) the same drugs used to treat RA were generally used to treat IBD using the same or similar dosing regimens; and (3) the TNF-α inhibitor infliximab was known to be efficacious in the treatment of RA and IBD (including UC) at the same doses and dosing regimens.

A POSA's reasonable expectation of success would also have been supported by the FDA-approved labels for Remicade® which showed, with clinical trial data, that a range of doses were effective in treating both RA and CD, including a $10^{mg}/_{kg}$ dose and an 8-week interval dosing period. Ex.1051 at 1085-86. A POSA would have understood from the Remicade® clinical trial data that there was a reasonable expectation that other anti-TNF-α drug products, such as D2E7, would be effective in treating both RA and IBD (including both UC and CD) with the same dose and dosing regimen.

9. The Prior Art Combination Described Above Renders Obvious Claims 1-6 of the '790 Patent

Claims 1-2 of the '790 patent are obvious over the prior art for the reasons stated *supra* VI.C.1–VI.C.8.

Claim 3 depends from claim 1 and recites that "the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody." Ex.1001. Salfeld described and placed in the prior art the benefits of administering the "entirely human" D2E7 antibody over chimeric or humanized antibodies (which "still retain some murine sequences") in avoiding "an unwanted immune reaction." Ex.1006***** at 4:5-15. Accordingly, it would have been obvious to administer the prior art "entirely human" D2E7 antibody to treat UC in a patient who had a previous unwanted immune response to a chimeric or humanized anti-TNF-α antibody. *Id.*

Claims 4, 5, and 6, recite the limitation "wherein the human anti-TNFα antibody is administered for a period at least 24 weeks." Ex.1001.

As Bjarnason explains, it was well known that UC and CD were both chronic conditions that in certain patients required treatment with an anti-IBD therapeutic for periods of at least 24 weeks. Ex.1008 at ¶¶132-33; Ex.1117 at 184 (describing 5 azathioprine trials to treat UC for periods of 3, 6, 6, 12 and 12 months, respectively); Ex.1005 at 126 (citing ex.1024 at A1078 (describing a study by Rutgeerts in which patients with CD received an initial dose of infliximab, followed by $10^{mg}/_{kg}$ infliximab at 12, 20, 28 and 36 weeks) and ex.1022 at 101 (describing an IBD case series by van Dullemen involving infliximab treatment over a 24 week period)). Although the UC data, unlike the RA and CD data, for anti-TNF-α treatment is based on a single infusion, a POSA would understand that repeat dosing would likely result in maintenance of the beneficial effect based on the totality of the data for RA, CD and UC and the common TNF-α origin of these chronic inflammatory disorders. Ex.1008 at ¶133; Ex.1116 at 1034 ("It seems likely that either repeat dosing or a higher initial dose would be needed to provide further maintenance of this beneficial effect" from a "single infusion of 5 $^{mg}/_{kg}$ CDP571" in UC patients.); Ex.1005 at 129 (stating that for the treatment of UC with infliximab, additional studies are needed "to determine optimal dose and dosing intervals.").

Accordingly, claims 4, 5 and 6 are obvious over the prior art.

D. Ground 2: Salfeld in Combination With VDP2000 and Rau, in View of Sandborn, Render Claims 1-6 Obvious

In *BI408*, the Board found all claims of the '135 patent invalid as obvious over the combination of VDP2000 and Rau. *BI408* at 44. VDP2000 has the same disclosure as VDP1999 and further provides data for up to six months (*i.e.*, 24 weeks) of treatment. Rau describes the same studies as Kempeni and VDP1999, and additionally concludes, "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." Ex.1017***** at 8. For the same reasons as discussed above with respect to VDP1999 and Kempeni, 40mg D2E7 eow dosing to treat RA is obvious over VDP2000 and Rau. This conclusion of obviousness is only bolstered by the additional disclosures of VDP2000 and Rau.

As Posner explains, based on Rau's express teaching of subcutaneous, eow dosing of D2E7, as well as the drug's 12-day half-life, a POSA would be motivated to modify VDP2000's 20mg weekly dose to arrive at a subcutaneous, 40mg eow D2E7 dosing regimen, and would have a reasonable expectation of success in so doing. Ex.1015 at ¶¶69-74. VDP2000 and Rau collectively disclose each limitation of the '135 claims. *Id.* at ¶70; *BI408* at 15. VDP2000 discloses all of the elements of the '135 claimed regimen except for eow dosing. Ex.1015 at

¶60; *BI408* at 15. Rau expressly teaches eow, subcutaneous dosing of D2E7 to treat RA. Ex.1015 at ¶¶63-64; *BI408* at 17-18.

A POSA would understand that the 20mg D2E7 weekly dose disclosed by VDP2000 treated RA as required by the '135 claims. VDP2000 teaches that all of its doses of D2E7 were "statistically significantly superior to placebo," and that "20, 40 and 80 $^{mg}/_{week}$ were statistically equally efficacious when given s.c. in patients with active RA." Ex.1107***** at 2. It further discloses that 49% of patients on the 20mg D2E7 dose achieved an ACR20 response at month 3, compared with only 10% of placebo-treated patients. *Id.* A POSA would understand that this level of ACR20 response over placebo (39% increase) demonstrates clinical efficacy for the 20mg D2E7 weekly dose. Ex.1002 at ¶34. This conclusion is consistent with the FDA's approval of Remicade® for RA in which, based on a 30-38% increase in patients achieving ACR20 with Remicade® as compared to placebo, the FDA concluded that "[a]ll of the dosing regimens evaluated . . . showed benefit as adjunctive therapy to MTX in the treatment of patients with rheumatoid arthritis." Ex.1111***** at 26; Ex.1002 at ¶34.

Any argument by AbbVie that the 20mg weekly D2E7 dose taught by VDP2000 was less effective than the 40 or 80mg doses should be rejected. Even apart from VDP2000's express teaching that all D2E7 doses evaluated were "statistically equally efficacious," Posner explains that the DE007 study reported

by VDP2000 was not designed to allow the POSA to draw reliable dose-to-dose comparisons. Ex.1015 at ¶94. Rather, additional statistical information would have been required to ensure that any numerical differences between dosing groups did not result from chance. *Id.*

Moreover, even if the POSA misread VDP2000 as disclosing that the 20mg dose was less effective than the other doses tested, the POSA would not ignore that dose, but would rather recognize that, as one of a finite number of effective doses reported, the 20mg dose was worth pursuing. *Id.* at ¶95.

Any argument that allegedly inferior efficacy of the weekly 20mg dose of VDP2000 would teach away from an analogous 40mg eow dose should also be rejected because the claims do not require that the *most* effective dose be used. Rather, the claims only require that the dosing regimen be "sufficient to treat" – *i.e.*, reduce the signs, symptoms, and/or progression of – RA. VDP2000's data clearly show that the 20mg dose reaches that threshold. Ex.1107***** at 2; Ex.1002 at ¶35.

Given that VDP2000 discloses that a 20mg, subcutaneous weekly D2E7 dose was one of a finite number of options effective to treat RA, the POSA would be motivated to investigate an analogous 40mg eow dose, in light of Rau. Ex.1015 at ¶95. Rau expressly teaches "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or

subcutaneously." Ex.1017***** at 8. Accordingly, Rau links the ~2 week half-life of D2E7 with an eow subcutaneous dosing regimen. The POSA would be motivated to pursue the eow dose analogous to the 20mg weekly dose disclosed in VDP2000. Ex.1015 at ¶95. Posner explains that the POSA would understand this analogous dose to be 40mg eow, based on the disclosed half-life of D2E7 and its known linear pharmacokinetics. *Id.* at ¶¶71-72. The POSA would understand that the total drug exposure (area under the curve of serum concentrations) during a 2 week interval following a single dose of 40mg D2E7 would be approximately equal to that following two 20mg doses administered a week apart over the same time interval. *Id.* at ¶72. This would suggest to the POSA, in view of VDP2000, that a 40mg eow dose would be enough to achieve clinical results. Rau, therefore would motivate the POSA to modify VDP2000's 20mg weekly dose to arrive at a 40mg eow dose and would provide a reasonable expectation of success in so doing. *Id.* at ¶74.

None of the arguments AbbVie asserted against the combination of VDP2000 and Rau during the *BI408* IPR change this conclusion. As explained by Posner and Helfgott, AbbVie's teaching away arguments should be rejected for the reasons discussed *supra* VI.C.6.c. Ex.1015 at Section IX; Ex.1002 at ¶¶48-64; *see BI408* at 26-38. AbbVie's argument that a POSA would avoid Rau's $0.5^{mg}/_{kg}$ D2E7 eow dosing regimen (equivalent to 40mg eow in an 80 kg patient) out of

concerns about efficacy is further belied by a later prior art study by Weisman, which tested an eow $0.5^{mg}/_{kg}$ dose of D2E7 (as well as a $0.25^{mg}/_{kg}$ dose), and concluded that D2E7 "is well tolerated, safe and efficacious when given in combination with [methotrexate] in patients with longstanding RA." Ex.1108***** at 5; Ex.1002 at ¶¶61-64; *BI408* at 32. As Helfgott explains, a POSA would not expect that AbbVie would further test the $0.5^{mg}/_{kg}$ biweekly dose, as it did in Weisman, if that dose had previously been determined to be ineffective. Ex.1002 at ¶64; *see BI408* at 32.

Accordingly, VDP2000 in combination with Rau render the 40mg eow RA regimen obvious. As explained *supra* VI.C.2 – VI.C.5, VI.C.9, the prior art additionally rendered obvious using this regimen to treat UC, as claimed in claims 1-6.

E. No Secondary Considerations Such As Commercial Success Demonstrate Nonobviousness

1. No Proof of Commercial Success

AbbVie has repeatedly made contradictory arguments of commercial success attempting to support the patentability of its varied portfolio of secondary D2E7-related patents. There can be no nexus between Humira®'s commercial success and the claims of the '790 patent because at different times AbbVie has attributed the commercial success of Humira® to entirely different patents. The Federal Circuit, however, has held that where one patent blocks market entry, any

commercial success enjoyed by the product cannot be convincingly attributed to other patents. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak."); *Coal. for Affordable Drugs II LLC v. NPS Pharm., Inc.*, No. IPR2015-01093, FWD, Paper No. 67, at 32 (Oct. 21, 2016) (holding there was no showing of commercial success where the Board could not "conclude from the evidence before [it] whether the sales are due to the merits of the invention of the [patent at issue] and not, for example, [a different patent].").

Because AbbVie, in different proceedings, has relied on conflicting evidence and has made inconsistent assertions pointing to different patents as the driver of Humira®'s commercial success, it has no basis for now arguing that it is the '790 patent that drives Humira®'s sales. For example, in defending the alleged patentability of a patent (U.S. Patent No. 8,916,158 (the "'158 patent")) claiming an adalimumab formulation against a petition for IPR, AbbVie argued that the commercial success of Humira® was "driven in large part by" its formulation. Ex.1035 at 28. If Humira®'s commercial success was "driven in large part" by the formulation, as AbbVie asserted, then there is no basis for it to argue now that it was largely driven by a 40mg eow dosing regimen for one of the many labeled indications, UC. Moreover, the very evidence that AbbVie submitted, supposedly

in support of its response to the ’158 formulation patent petition, acknowledged that the commercial success of Humira® was due to its initial patent on the D2E7 antibody itself: “Abbott loses its key patent on the composition of matter for Humira in 2016, meaning it could face competition from cheaper ‘biosimilar’ knockoffs.” Ex.1031***** at 5 (cited as ex.2003 in the ’158 IPR).

When trying to defend its RA dosing patents, AbbVie attributed Humira®’s commercial success, not to its UC dosing regimen, not to its formulation, and not (more plausibly) to D2E7 itself, but (more conveniently) to the RA dosing regimen. It argued that Humira®’s dosing “regimen . . . specifies the biological agent (D2E7), the method of administration (subcutaneous), the dose (40mg fixed dose) and the dosing interval (13-15 days).” Ex.1030 at 58.

In *Coherus*, the Board recognized that AbbVie has inconsistently argued that different attributes of Humira® have led to its commercial success in different proceedings: “[t]hus, Patent Owner has relied on features other than the dosing regimen recited in the ’135 patent claims as driving the commercial success of HUMIRA®.” *Coherus* at 40. The Board stated: “it is not clear whether the sales of HUMIRA® are due to the dosing regimen recited in the ’135 patent, or the formulation that Patent Owner argued was the driver of commercial success in another [IPR], or the known and patented fully human D2E7 antibody.” *Id.* at 41; *see BI408* at 41.

Accordingly, AbbVie cannot save the claims of the '790 patent from invalidity by asserting that the commercial success of Humira® is due to the methods claimed in the '790 patent, particularly when the teachings of the prior art so clearly render those methods obvious. *See, e.g.*, *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness. . . . Here, where the inventions represented no more than 'the predictable use of prior art elements according to their established functions,' the secondary considerations . . . are inadequate to establish nonobviousness as a matter of law.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007)) (citation omitted).

2. No Proof of Long-Felt Need and Failure of Others

In the '135 IPRs, AbbVie argued that "[t]here was a long-felt but unmet need for new RA therapies" with convenient dosing. Ex.1030 at 55; *see BI408* at 41 ("Patent Owner contends there was a long-felt need for new RA therapies supporting the nonobviousness of the challenged claims."). AbbVie argued that two anti-TNF-α agents used to treat RA (Enbrel® and Remicade®) were both inconvenient for patients. Ex.1030 at 55-56 (noting that Enbrel® requires two doses per week and Remicade® is administered intravenously instead of subcutaneously); *see BI408* at 41. However, biweekly dosing of D2E7 was already

disclosed by Kempeni (ex.1004 at I71) and Rau (ex.1017***** at 8) and the subcutaneous administration of D2E7 was already disclosed by each of VDP1999, Kempeni, VDP2000 and Rau. Ex.1003***** at 3, Ex.1004 at I71-72; Ex.1017***** at 7; Ex.1107***** at 2; *see Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015) ("If commercial success is due to an element in the prior art, no nexus exists.") (internal quotation marks omitted).

Additionally, AbbVie previously argued that "[o]thers [sic] companies tried and failed to satisfy" a need for "additional biologics with more advantageous dosing regimens" and asserted that two drugs Roche and Celltech attempted to develop failed because they produced ADAs. Ex.1030 at 56. AbbVie did not offer any proof that the prior art actually recognized any such need. Moreover, AbbVie's argument fails because even if it could demonstrate such a recognized need, its alleged satisfaction of that need would be attributable to an inherent property of the prior art D2E7 antibody (ex.1004 at I70) which had been protected by the now expired '382 patent. *See Coal. for Affordable Drugs II LLC*, IPR2015-01093, at 33 (holding that where the "Patent Owner does not provide evidence sufficient to permit a determination as to whether the long-felt need was met by the [patented invention] . . . the record . . . does not sufficiently indicate that the claimed subject matter itself satisfied a long-felt need.").

For similar reasons in *Coherus*, *BI409* and *BI408* the Board rejected AbbVie's "long-felt need" arguments. *Coherus* at 41-43; *BI409* at 43-45, *BI408* at 41-43.

F. Summary

The claim charts below identify where in the prior art each of the claim limitations are found.

Independent Claim

Claim Language of the '790 Patent	**Prior Art Disclosures**	
Claim 1		
	Ground 1	**Ground 2**
A method for treating ulcerative colitis in a human subject,	See below.	See below.
comprising administering subcutaneously to a human subject	"The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular)." Ex.1006***** at 30:4-6. "Patients were randomised equally into four arms to receive weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." Ex.1003***** at 3.	Ex.1006***** at 30:4-6. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 . . . can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." Ex.1017***** at 8.

Claim Language of the '790 Patent	Prior Art Disclosures	
	"The safety and efficacy of weekly subcutaneous administration of 0.5 $^{mg}/_{kg}$ D2E7 was evaluated . . . ." Ex.1004 at I71.	
having ulcerative colitis	"The human antibodies . . . of the invention can be used to treat autoimmune diseases, in particular those associated with inflammation, including rheumatoid arthritis . . . ." Ex.1006***** at 39:13-15. "The human antibodies, . . . of the invention, also can be used to treat . . . idiopathic inflammatory bowel disease, which includes two syndromes, Crohn's disease and ulcerative colitis." Ex.1006***** at 41:20-23.	
a total body dose of 40 mg of a human anti-TNFα antibody	"Patients were randomised equally into four arms to receive weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." Ex.1003***** at 3.	Ex.1107***** at 2 (same as ex.1003***** at 3).
once every 13-15 days	"D2E7 was administered every two weeks until responses could be rated as 'good', defined as an absolute DAS of < 2.4." Ex.1004 at I71.	"D2E7 . . . can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." Ex.1017***** at 8.
for a time period sufficient to treat the ulcerative colitis,	"The human antibodies, . . . of the invention, also can be used to treat . . . idiopathic inflammatory bowel disease, which includes two syndromes, Crohn's disease and ulcerative colitis." Ex.1006***** at 41:20-23.	

Claim Language of the '790 Patent	**Prior Art Disclosures**	
wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region;	"[A]n anti-TNFα antibody or antibody portion of the invention is administered to a human subject . . . ." Ex.1006***** at 38:27-28. "In certain embodiments, the antibody has an IgG1 heavy chain constant region . . . ." Ex.1006***** at 6:31-32.	
a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7,	"[T]he LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7 . . . ." Ex.1006***** at 6:25-27. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3. "[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	Ex.1006***** at 6:25-27. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.
a CDR2 having the amino acid sequence of SEQ ID NO:5,	"[T]he LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5. . . ." Ex.1006***** at 6:23-24. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3.	Ex.1006***** at 6:23-24. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.

Claim Language of the '790 Patent	Prior Art Disclosures	
	"[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	
and a CDR3 having the amino acid sequence of SEQ ID NO:3	"The most preferred recombinant antibody of the invention, termed D2E7, has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3 . . . ." Ex.1006***** at 5:19-21. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3. "[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	Ex.1006***** at 5:19-21. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.
and a variable heavy ("V_H") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 8,	"[T]he HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8." Ex.1006***** at 6:26-27. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3.	Ex.1006***** at 6:26-27. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.

Claim Language of the '790 Patent	Prior Art Disclosures	
	"[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	
a CDR2 having the amino acid sequence of SEQ ID NO:6	"[T]he HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6." Ex.1006***** at 6:24-25. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3. "[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	Ex.1006***** at 6:24-25. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.
and a CDR3 having the amino acid sequence of SEQ ID NO:4.	"The most preferred recombinant antibody of the invention, termed D2E7, has a . . . heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4." Ex.1006***** at 5:19-21. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003*****	Ex.1006***** at 5:19-21. Ex.1107***** at 2 (same as ex.1003***** at 3). "D2E7 is . . . effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.

Claim Language of the '790 Patent	Prior Art Disclosures	
	at 3. "[P]atients were treated with single doses of D2E7 . . . ." Ex.1004 at I71.	

Dependent Claims

Claim Language of the '790 Patent	Prior Art Disclosures	
Claim 2		
	Ground 1	**Ground 2**
The method of claim **1**, wherein the V_L chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:1 and the V_H chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:2.	"Preferably, the D2E7 antibody has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2." Ex.1006***** at 5:22-24. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1003***** at 3. "[P]atients were treated with single doses of D2E7. . . ." Ex.1004 at I71.	Ex.1006***** at 5:22-24. "Patients were randomised equally into four arms to receive weekly doses of . . . D2E7 . . . ." Ex.1107***** at 2. "D2E7 is …effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment . . . ." Ex.1017***** at 8.

Claim Language of the '790 Patent	Prior Art Disclosures	
Claim 3		
	Ground 1	**Ground 2**
The method of claim **1**, wherein the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody.	"[H]umanized antibodies, in which the hypervariable domains of the antibody variable regions are murine-derived but the remainder of the variable regions and the antibody constant regions are human-derived, have also been prepared. However, because these chimeric and humanized antibodies still retain some murine sequences, they still may elicit an unwanted immune reaction . . . ." Ex.1006***** at 4:5-11 (citations omitted).	
Claims 4-6		
	Ground 1	**Ground 2**
Claim 4: The method of claim **3**, wherein the human anti-TNFα antibody is administered for a period of at least 24 weeks.	*See supra* VI.C.9; ex.1005 at 126 (discussing studies to treat IBD that administered therapeutics for at least 24 weeks).	
Claim 5: The method of claim **2**, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks.		
Claim 6: The method of claim **1**, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks.		

VII. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that claims 1-6 of the '790 patent are unpatentable as obvious in view of the prior art identified herein. Petitioner therefore requests that the Board institute *inter partes* review for each of those claims.

Dated: August 21, 2017

Respectfully submitted,
/s/ David K. Barr
David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer LLP
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 C.F.R. §42.24(a)(1)(i). Exclusive of the portions exempted by 37 CFR 42.24(a), this Petition contains 13,990 words as counted by the word processing program used for its preparation (Microsoft Word 2010).

The undersigned further certifies that this brief complies with the typeface requirements of 37 C.F.R. §42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. §42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Dated: August 21, 2017

/s/ David K. Barr

David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Sandoz Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 8,974,790 and Exhibits 1001 – 1129 were served on August 21, 2017 via U.S. Mail to the correspondence address for the attorney of record for AbbVie Biotechnology Ltd., the assignee of the '790 patent.

Dechert LLP
1095 Avenue of the Americas
New York, NY 10036-6797

Dated: August 21, 2017

/s/ David K. Barr
David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560